MEDICAL LIBRARY

VOL. 190, No. 5 NOVEMBER, 1935 NOV 5 1935 No. 764

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

E. B. KRUMBHAAR, M.D., EDITOR
RICHARD A. KERN, M.D., ASSISTANT EDITOR

ESTABLISHED 1820

INFLAMMATION AND BACTERIAL INVASIVENESS. By VALY MENKIN, M.D. . . . 583

VARIATIONS IN THE GASTRIC MUCOSA IN PERNICIOUS ANEMIA: GASTROSCOPIC, SURGICAL AND ROENTGENOLOGIC OBSERVATIONS. By CHESTER M. JONES, M.D., E. B. BENEDICT, M.D., and A. O. HAMPTON, M.D. 596

DISTRIBUTION OF THE ERYTHROCYTE POPULATION IN REGARD TO DIAMETERS AND OSMOTIC RESISTANCE IN SPLENECTOMIZED CASES OF HEMOLYTIC ICTERUS. A CONTRIBUTION TO AN UNDERSTANDING OF THE PATHOGENESIS OF THE DISEASE. By DR. G. MOMIGLIANO-LEVI and DR. A. BAIRATI 610

BIOPSY OF THE STERNAL BONE MARROW. ITS VALUE IN THE STUDY OF DISEASES OF BLOOD-FORMING ORGANS. By WILLIAM DAMESHEK, M.D. 617

SYSTEMATIC VARIATION IN THE HUMAN MENSTRUAL INTERVAL. By OSCAR W. RICHARDS, PH.D. 641

THE DAILY REQUIREMENT IN HUMAN HYPOTHYROIDISM OF PURIFIED HUMAN THYROID HORMONE AT VARIOUS METABOLIC LEVELS. A COMPARISON BETWEEN SPONTANEOUS MYXEDEMA AND CACHEXIA STRUMIPRIVA. By EUGENE C. EPPINGER, M.D., and WILLIAM T. SALTER, M.D. 649

STUDIES OF GALL-BLADDER FUNCTION. XII. THE COMPOSITION OF "WHITE BILE" By CECILIA RIEGEL, PH.D., I. S. RAVDIN, M.D., CHARLES G. JOHNSTON, M.D., and PHILIP J. MORRISON, A.B. 655

THE DISTRIBUTION AND PROGNOSIS OF PULMONARY LESIONS. ASSOCIATED TUBERCULOUS AND NON-TUBERCULOUS. By F. MAURICE McPHEDRAN, M.B. (TOR.) . 659

ELECTROCARDIOGRAPHIC CHANGES DURING ENCEPHALOGRAPHY (20 CASES). By MILTON M. ABELES, M.D., and DANIEL E. SCHNEIDER, M.D. 673

FURTHER STUDIES IN CALCIUM AND PARATHYROID THERAPY IN CHRONIC ULCERATIVE COLITIS. By BENJAMIN HASKELL, M.D., and ABRAHAM CANTAROW, M.D. 676

DIABETIC COMA WITH EXTREME HYPERGLYCEMIA. By EDWARD S. DILLON, M.D., and W. WALLACE DYER, M.D. 683

THE METABOLISM OF GALACTOSE. III. THE INFLUENCE OF DISTURBED ENDOCRINE FUNCTION. By ALLAN WINTER ROWE, PH.D. 686

THE METABOLISM OF GALACTOSE. VII. THE INFLUENCE ON TOLERANCE OF COEXISTING ENDOCRINOPATHIES. By ALLAN WINTER ROWE, PH.D. . . . 701

INDEX TO PHYSICIAN'S SUPPLIES . . . . . ADV. PAGE 42

Contents continued on adv. page 14

OWNERS AND PUBLISHERS
LEA & FEBIGER
PHILADELPHIA

COPYRIGHT, 1935, BY LEA & FEBIGER. ALL RIGHTS RESERVED. ENTERED AT THE POST-OFFICE AT PHILADELPHIA AS SECOND-CLASS MATTER

PUBLISHED MONTHLY. SUBSCRIPTION, SIX DOLLARS A YEAR.

PROLONG LIFE
in cases of hypertension

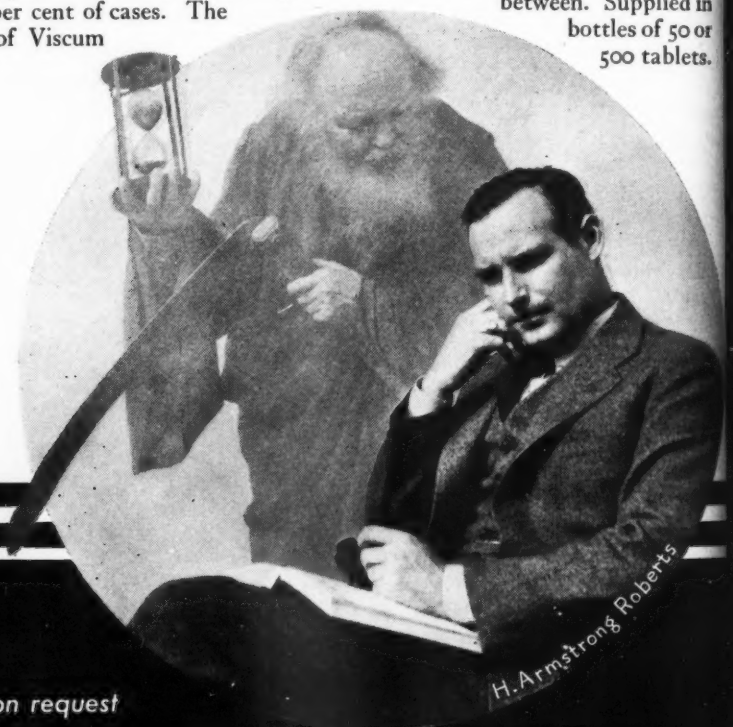
By easing the heavy burden of high blood-pressure upon the heart and kidneys, you can postpone the advent of the Grim Reaper for many years.

Reduce blood-pressure quickly and effectively by prescribing Hepvisc, the synergistic combination of Viscum album with hepatic and insulin-free pancreatic extracts. It often lowers the reading on the sphygmomanometer 20 to 30 mm. Hg. in 4 to 12 hours.

Headache and dizziness associated with hypertension are relieved early in 75 per cent of cases. The value of Viscum album in checking these symptoms has been demonstrated by O'Hare and Hoyt (*New England J. Med.*, 199: 1207, 1928) and also by Barrow (*California and Western Med.*, 33: 887, 1930).

Hepvisc is especially indicated for treatment of essential hypertension, and is also beneficial in cases of high blood-pressure due to pregnancy or fibrosis of the kidneys.

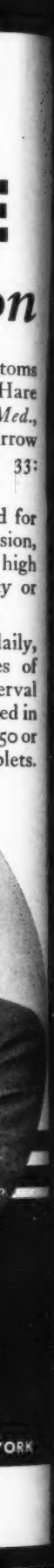
Prescribe 3 to 6 tablets daily, ½ hour before meals, in courses of 2 to 3 weeks with a week's interval between. Supplied in bottles of 50 or 500 tablets.



Samples on request

HEPVISC **TAKES THE LOAD OFF HEART AND KIDNEYS**

ANGLO-FRENCH DRUG CO. (U.S.A.) INC. 1270 BROADWAY, NEW YORK



THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

NOVEMBER, 1935

ORIGINAL ARTICLES.

INFLAMMATION AND BACTERIAL INVASIVENESS.*†

By Valy Menkin, M.D.,

INSTRUCTOR IN PATHOLOGY, HARVARD UNIVERSITY MEDICAL SCHOOL, BOSTON, MASS.

I propose to discuss some observations gathered during the past few years concerning the relationship of inflammation to immunity.

Inflammation, broadly defined, is the complex vascular, lymphatic, and general tissue response to the presence of an irritant. The development of the inflammatory reaction consists of a series of dynamic and sequential changes which tend to localize and ultimately dispose of this irritant. It is with a study of some of these changes that we have been engaged.

Several years ago it was found that when a vital dye, trypan blue, is injected directly into the subcutaneous tissues of a rabbit, the dye rapidly diffuses into the tributary lymphatics, so that if these regional vessels are cannulated, the lymph is stained intensely with the dye. If, on the other hand, the same dye is injected into a prepared area of inflammation induced by a chemical irritant such as aleuronat, the dye fails to penetrate to either the draining lymphatic vessels or the regional lymph node.[1] The dye has evidently been *fixed* in the inflamed area. Furthermore it was observed that there is an important time relationship in this connection. The dye was found fixed as early as 30 minutes after the subcutaneous injection of aleuronat as an irritant. I shall refer to this fact later on, and to the importance of this early retention of foreign substances at the site of an acute inflammation. Subsequent experiments showed that the intravenous injection of this dye is followed

* Address delivered before the Philadelphia Pathological Society, March 14, 1935.

† These studies were aided by grants from the DeLamar Mobile and the Wellington Memorial Research Funds.

by a rapid accumulation of trypan blue in the inflamed focus. Studies revealed that this accumulation is in part due to the increased capillary permeability in inflammation, and also, as just pointed out, to the inability of the dye to drain outward into the regional lymphatics.

The extent of increased plasma filtration due to capillary injury and increased capillary pressure at a point of injury is open to quantitative measurements.[2] By means of a vital dye, it was shown that with certain inflammatory irritants the normal permeability of capillaries is increased about twofold.* Particulate matter which is unable to pass through the normal capillary endothelium readily passes through the lining of such channels in an inflamed area.[3] The increased permeability of capillaries in inflammation is an initial reaction. It has been detected as early as 2 minutes after the injection of certain irritants.

These findings are applicable to microörganisms. When bacteria such as B. prodigiosus or B. pyocyaneus, are injected into the circulating blood stream, they localize and are recovered from foci of inflammation in greater numbers than from surrounding normal tissues. This was found by culturing inflamed skin areas and by comparing the number of colonies obtained with those recovered from corresponding normal cutaneous regions. Bacteria when injected directly into an area of injury are likewise fixed *in situ* precisely as in the case of the vital dye described previously, and these microörganisms fail to disseminate to the tributary lymphatics as readily as they do under normal circumstances. The frequent localization of bacteria from the blood stream in a *locus minoris resistentiæ*, after preliminary trauma or other injury to tissue, is well known to pathologists and clinicians. Osteomyelitic conditions are the frequent consequences of such preliminary injury. My observations on the accumulation of bacteria in an inflamed area from the circulating blood stream may explain the mechanism of this phenomenon in terms of increased capillary permeability with subsequent accumulation and fixation of bacteria at the point of injury.[3]

Since antibodies are regarded as being closely associated with globulins, the demonstration of an increased concentration and of a retention in inflamed tissue of foreign proteins from the blood stream would obviously be significant in connection with the rôle of antibodies in specific infectious processes. A series of experiments revealed that horse serum injected into the circulation accumulates at the site of an acute inflammation from which it fails to

* The term "permeability" as employed in this discussion and in previous communications refers to the degree of filtration through the capillary wall. It is, however, understood that the increased filtration in acute inflammation involves as one of its most important factors an injury to the endothelial wall with increased permeability of the membrane as indicated by the passage of particulate matter.

drain away readily.[4] The fixation of this foreign protein was found to be distinctly more pronounced in inflamed cutaneous tissue than in a corresponding irritated perionteal cavity. These observations formed the basis for an explanation of the local anaphylactic phenomenon described several years ago in the ear of the rabbit by Auer.[4,5]

Shwartzman described the reaction that occurs when a filtrate of B. typhosus is injected into the skin of a rabbit. Twenty-four hours later when the same filtrate or a filtrate of a non-related organism, such as the meningococcus, is introduced into the circulating blood, hemorrhagic necrosis frequently appears at the site of the cutaneous injection.[6] In 1931, on the basis of the aforementioned studies on the accumulation and fixation of foreign proteins at the site of inflammation, I suggested that the intense cutaneous reaction following the intravenous injection of a bacterial filtrate may be the result of an accumulation of this substance in an area of skin already inflamed.[7] The reaction does not necessarily have to take place with all bacterial filtrates or with all types of inflammatory irritants. The degree of permeability of the capillaries and the optimum synergistic action of two irritating substances on one another may modify the final manifestation. That the bacterial filtrate or other reacting material which is injected intravenously in order to induce the local skin reaction, may be chemically altered while in the circulation is perfectly possible. However this in no way modifies my original suggestion that the Shwartzman phenomenon may be conceived of as a non-specific reaction resulting from the accumulation in an inflamed area of an irritating substance. Sickles demonstrated that, following the cutaneous injection of a bacterial filtrate, intravenous injection of agar produces the typical hemorrhagic manifestation described by Shwartzman.[8] This observation is in accord with the view that the phenomenon is a non-specific reaction. The histological studies of Karsner and Moritz,[9] and the more recent work of Freund[10] on the guinea pig, where silver nitrate was employed as the preparatory factor, have essentially confirmed by original viewpoint.* It is interesting to note in this connection that, although Shwartzman himself believes that the explanation here offered is untenable, this investigator has as yet produced but meager evidence to disprove this hypothesis. By diluting the skin preparatory factor, Shwartzman notes no detectable inflammatory reaction by gross examination prior to the intravenous injection of the filtrate. And yet a striking hemorrhagic and necrotic lesion is often elicited several hours after the intravenous injection of the bacterial filtrate.[11] The absence of gross evidence of inflammation at the prepared skin site does not neces-

* It is to be noted that with the exception of Freund's work with silver nitrate in which he obtained the Shwartzman reaction in about half of his guinea pigs, the skin preparatory factor has in all cases been a bacterial filtrate.[11]

sarily indicate that the capillary wall is normal. As previously pointed out,[12] the increase in the permeability of capillaries in inflammation may occur extremely early and may in many instances produce little, if any, change that is detectable by gross or even microscopic examination. An increase in the functional filtration through the capillary endothelium, as indicated not necessarily by morphological evidence, but rather by the ability of foreign materials from the blood stream to accumulate in the prepared area, would adequately explain the Shwartzman phenomenon as a type of inflammatory reaction induced by the superimposition of an irritant concentrating from the circulating blood in a previously inflamed area.

The studies on accumulation and fixation of foreign proteins in inflamed tissue suggest perhaps a possible explanation for the phenomenon of the focal reaction in tuberculosis. When tuberculin is introduced into the blood stream of an animal with a tuberculous lesion, an intense inflammatory reaction may develop in the lesion. The mechanism of this focal reaction in tuberculosis is not understood. It is conceivable, in view of the experiments with horse serum, that in a like manner, tuberculoprotein may accumulate from the blood stream in the inflamed tuberculous lesion and, by its presence there, induce a local inflammatory reaction.

As was pointed out 3 years ago, these studies on proteins suggest the important rôle which circulating antibodies may play in the early stages of specific inflammatory reactions. For by their accumulation and fixation in such foci they doubtless play a significant part in reinforcing cellular factors which ultimately dispose of the irritant.[13] The earlier studies of Opie on the Arthus phenomenon demonstrated clearly the protective action resulting from the fixation of the antigen at the site of the anaphylactic inflammation.[14] In this connection the recent interesting work of Rich and McKee[15] is noteworthy. These investigators showed that following the cutaneous reinoculation of pneumococcus Type I in animals immunized to that organism, an agglutinative response occurred in the tissue. It remains to be seen whether the agglutinative elements described by these workers are not in part the result of a concentration in the skin of antibodies from the circulating blood stream, owing to an increased capillary permeability following bacterial inoculation.

The mechanism of *fixation* whereby foreign substances or bacteria fail to disseminate readily from an acutely inflamed focus is referred primarily to an obstructive barrier in the form of thrombosed lymphatics and coagulated plasma in tissues distended with edema.[16] Time does not permit description of the various experiments to substantiate this concept. The important evidences in this connection will be mentioned briefly.

In the first place phagocytosis does not play a significant rôle

in the reaction of fixation. This phenomenon occurs so early after the introduction of an irritant that there are still relatively few leukocytes present at the time. Furthermore microscopic studies at this period fail to reveal any trace of the phagocytosed material tested. Yet these foreign substances are prevented from reaching the regional lymph nodes.

Microscopic examination of such acutely inflamed areas reveals a tissue distended with coagulated plasma. The presence of a fibrinous meshwork forms a conspicuous feature of the injured part. Careful observation of small vessels invariably brings to view many of the lymphatics either completely or largely occluded by thrombi consisting of a delicate fibrinous reticulum. In the later stages of the reaction, many leukocytes are found embedded in its meshes.

Subsequent experimental evidences substantiated this concept of mechanical obstruction to account for the inability of foreign substances or bacteria to disseminate from an inflamed focus. For instance, it was reasoned that if this were the case, a testing substance, such as a dye or bacteria, would, when injected at the periphery of an inflamed area, fail to enter it. This was found to be the case.[3,16]

The concept of mechanical obstruction was further established by a chemical test. Concentrated urea *in vitro* prevents the coagulation of blood, owing to its protein solvent action on fibrin. Preformed fibrin also tends to go into solution fairly readily in the presence of a sufficiently concentrated solution of urea crystals. When this substance is injected into a rabbit simultaneously with an inflammatory irritant, the reaction of fixation is inhibited. In such experiments the lymphatics are found unoccluded by thrombi, thus adequately accounting for the free drainage of substances from the inflamed area.[13]

The foregoing observations have offered a means of studying the mechanism to account for the differences in the invasive ability of various pyogenic organisms.[12,17]

The intensity and rapidity with which an inflammatory irritant is circumscribed in a tissue area varies with the type of irritant. The speed with which an irritant causes a region to be walled-off by mechanical obstruction in the form of thrombosed lymphatics or a fibrinous network or both is necessarily an important index in determining its ability to disseminate ultimately into the circulating blood. This holds true if the irritant *per se* can readily drain through lymphatic vessels from the site of inoculation. That bacteria disseminate from the site of inoculation through lymphatics has been frequently demonstrated. It follows from this that if bacteria are employed as inflammatory irritants some information may be obtained concerning the invasive capacities of different microorganisms. This would depend on the type of inflammatory reaction which a given microörganism induces in the host. Pathologists

and surgeons are familiar enough with the localizing tendency of staphylococcus in contrast to the invasive property of the streptococcus. Can the behavior of various pyogenic organisms in tissues be related at least in part to their respective abilities of creating an early inflammatory reaction at the site of their inoculation which would tend to prevent, by the mechanism previously described, their dissemination to the tributary lymphatic nodes? It has been pointed out in a former communication that when a vital dye is introduced into an area at various intervals of time after bacterial inoculation of this site, the degree of walling-off of the infected focus may be determined by the extent to which the dye can drain into the regional lymphatics or, for that matter, ultimately into the blood stream. This method can perhaps be used as a clinical test to determine the patency of lymphatics, or, in other words, the degree of walling-off of an area of inflammation such as a pyogenic abscess or an inflammatory reaction in a cavity, whether the peritoneal, pleural, or joint cavity.

The observations presently to be described represent a comparison of three pyogenic cocci: *S. aureus, Strep. hemolyticus,* and Type I pneumococcus with regard to the rapidity of retention of trypan blue at inflammatory foci induced by these respective organisms.[12] The significance of such data in regard to an understanding of the invasive properties of these microörganisms will be pointed out.

When trypan blue is injected into the skin of a rabbit immediately after the inoculation of *Staph. aureus,* the dye readily diffuses to the regional lymphatics. If, however, an interval of only 1 hour elapses between the injection of the bacterial irritant and that of the dye, the latter fails to drain into the lymphatics. An area of inflammation induced by the staphylococcus organism becomes evidently very rapidly circumscribed. Microscopic studies fully substantiate this fact for lymphatic lumina are found occluded by fibrinous thrombi. In many areas, the injured tissues are distended by coagulated plasma.

In the case of Type I pneumococcus, the dye continues to reach the lymphatic nodes until a somewhat later stage, *i. e.,* about 6 hours after the inoculation of the microörganisms. Here again this observation is correlated by the finding of occluding thrombi in lymphatics. It is of interest to note the absence of fibrin in the extracapillary spaces of the skin of these infected rabbits.

The prompt walling-off response on the part of staphylococcus is contrasted with the delayed reaction of fixation in the case of the hemolytic streptococcus. When these organisms are inoculated into the cutaneous tissues of rabbits, trypan blue freely drains from the site of bacterial inoculation to the regional lymphatic vessels for almost 2 days. Throughout this period the lymphatics are patent, as evidenced both by their normal functioning and by

the distended and almost unoccluded state of their lumina. About 45 to 50 hours after the initial inoculation of the streptococcus, microscopic examination reveals plugging of lymphatics by dense leukocytic thrombi. At this time the area of inflammation is effectively circumscribed, for trypan blue injected into such an area is fixed and is unable to drain to the regional lymphatic nodes. These observations, recently confirmed by Dennis and Berberian,[19] present an interesting paradox. Staphylococci produce in general little systemic effect owing to their intense local injurious reaction which fixes them *in situ*. Streptococci produce profound generalized effects on the organism as a whole because of their comparatively mild local reaction which allows them a relatively free penetration to the essential organs.

It is improbable that the interesting observations of Tillett and Garner on the fibrinolytic activity of hemolytic streptococci can offer an adequate explanation for this delayed fixation of trypan blue.[18] Their own findings definitely show that this lytic effect fails to take place with the plasma clot of the rabbit which was the animal used in our studies. It is noteworthy that Dennis and Berberian have attributed the delay of the inflammatory fixation in the presence of streptococci to the production of fibrinolytic substances.[19] Further studies, however, have caused these investigators to abandon this explanation.[20]

It is more likely that in the case of human streptococcal infection the dissolution of fibrin acts as a synergistic agent to a more fundamental factor which holds true for both human and rodent types of infection.

Studies now in progress support this point of view. The Berkefeld filtrates of several-days-old broth cultures of *S. aureus* induce an acute inflammatory reaction in the skin of rabbits which promptly causes retention of trypan blue (Table 1, Fig. 1).* The reaction is essentially indistinguishable from that obtained when the microörganisms alone are injected. Heating the filtrate to 58° C for about 1 hour destroys the principle responsible for the reaction (Table 2, Fig. 2). The filtrate of a day-old culture is ineffective, whereas the day old culture of the organisms produces perfect walling-off of the inflamed area. This indicates that the *S. aureus* owes its necrotizing activity (which doubtless is an important factor in its ultimate localization) not merely to its presence *per se*, but in addition also to its ability to release a powerful exotoxin-like product. This soluble toxic, thermolabile material is capable of inducing sufficient capillary and lymphatic damage to produce a shunting off, so to speak, of the inflamed area.

* The technique used in these experiments has been adequately described previously.[12] In brief 2.5 cc. of 1% trypan blue in saline is injected in the foreleg of a rabbit in a previously inflamed area induced in the above experiments by bacterial filtrates. About 2 hours later the regional lymphatics are examined for the presence of the dye.[1]

TABLE 1.—RETENTION OF TRYPAN BLUE AT SITE OF INFLAMMATION INDUCED BY FILTRATE OF STAPHYLOCOCCUS CULTURE.

Rabbit No.	Interval between injection of irritant and that of dye.	Total duration of inflammation.	Presence of dye on inflamed side.		Presence of dye on normal side.	
			Lymph of efferent lymphatic.	Lymph node.	Lymph of efferent lymphatic.	Lymph node.
	Hrs. Mins.	*Hrs. Mins.*				
8–35	1.05	3.50	0	0	+	+
8–34	1.36	4.48	0	0	+	+
8–22	1.40	4.25	0	0	+	+
8–83	2.35	5.12	0	0	++	++
8–31	19.42	22.02	0	0	+	+
8–85	19.44	22.24	0	0	++	+++
98	20.20	22.50	0	0	Faint trace	+
9–74	22.28	24.39	+ to ++	+	+	++++
10–12	22.55	24.05	0	0	Trace to +	Trace to +

TABLE 2.—RETENTION OF TRYPAN BLUE AT SITE OF INFLAMMATION INDUCED BY HEAT-INACTIVATED FILTRATE OF STAPHYLOCOCCUS CULTURE.

Experiment No.	Type of staphylococcus filtrate.	Interval between injection of irritant and that of dye.	Total duration of inflammation.	Presence of dye on inflamed side.		Presence of dye on normal side.	
				Lymph of efferent lymphatic.	Lymph node.	Lymph of efferent lymphatic.	Lymph node.
		Hrs. Mins.	*Hrs. Mins.*				
1	Inactivated	17.50	20.55	+++	++	++	+++
	Normal	17.45	21.00	+	+	++++	+++
2	Inactivated	18.05	20.20	++	++	++	+
	Normal	17.55	20.20	Trace	0	+	++
3	Inactivated	20.10	22.25	++	+	++	+
	Normal	20.00	22.20	Faint trace	0	+	+
4	Inactivated	20.40	23.10	++	++	++	+
	Normal	20.33	23.05	Trace	(?) Faint trace	+	+
5	Inactivated	25.25	27.10	+++	++	+++	++
	Normal	25.43	27.35	+	+	++	+++

There is some evidence that this material resembles in many respects staphylococcus leukocidin.

In the earlier studies of Denys and Van de Velde[21] these investigators pointed out that the action of staphylococcus leukocidin is not restricted solely to leukocytes, but that this material is injurious likewise to eosinophils, hematoblasts, red cells, and cells of

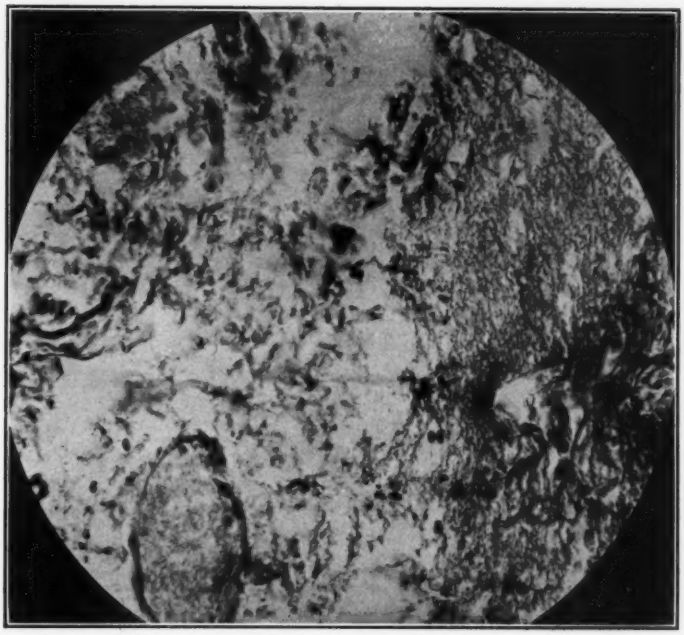


FIG. 1.—An inflamed area induced by the intracutaneuos inoculation of about 1.5 cc. of the Berkefeld filtrate of a several-day-old culture of *S. aureus* (See Rabbit 8-85, Table 1). The inflamed area is of over 22 hours' duration. Trypan blue injected into this area failed to reach the tributary lymphatics. Note both the fibrinous thrombus occluding the lymphatic lumen, and the coagulated plasma in the tissue spaces.

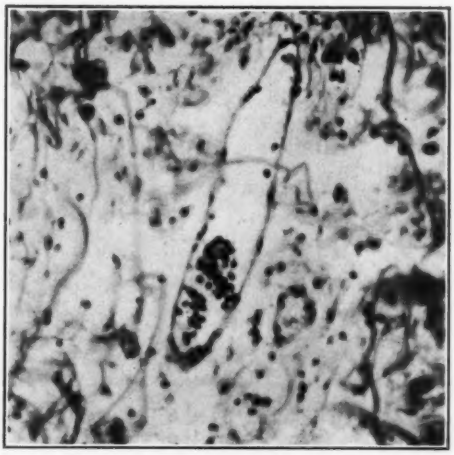


FIG. 2.—A lymphatic lumen in an area of inflammation induced by the inoculation of inactivated *S. aureus* filtrate. (This was accomplished by heating the filtrate at 58° C. for about 1 hour; see Exp. 5. Table 2.) The inflammation was of more than 27 hours' duration. The lumen is unoccluded. Trypan blue drained readily from this area to the tributary lymphatics.

UNIV. OF MICH.

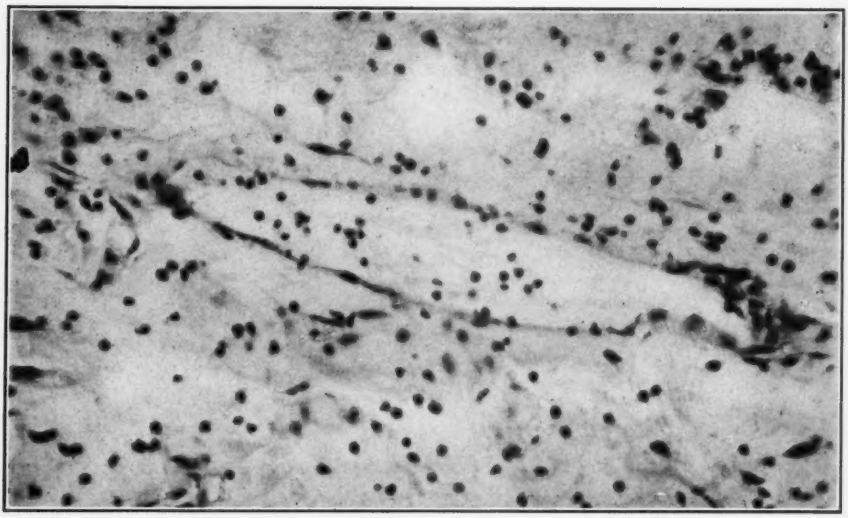


FIG. 3.—A lymphatic lumen in an area of inflammation induced by a Berkefeld filtrate of pneumococcus Type I. The inflammation is of more than 23 hours' duration (see Rabbit 8-77, Table 3). Note the unoccluded lumen in an area of edematous tissue with moderate cellular infiltration. Trypan blue readily diffused from such an area to the regional lymphatics.

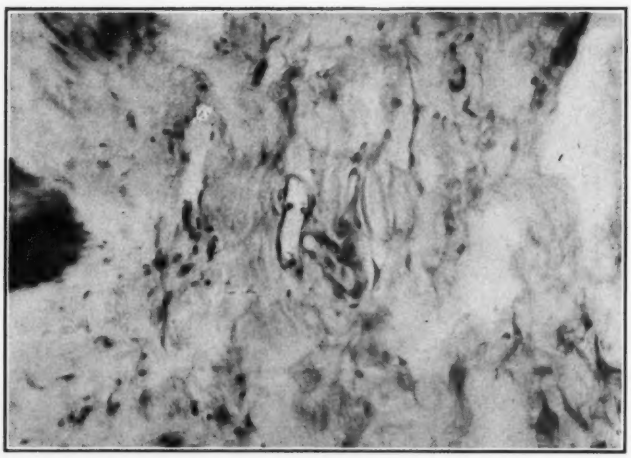


FIG. 4.—An inflamed area induced by the Berkefeld filtrate of a culture of hemolytic streptococci. The inflammation is of more than 52 hours' duration (see Rabbit X, Table 4). Note presence of unoccluded lymphatic lumina in tissue distended with edema. Typan blue diffused readily from this area to the regional lymphatics.

the sympathetic ganglia. Parker[22] in 1924 described the production of an exotoxin by certain strains of *S. aureus*. The Berkefeld filtrate of her strains revealed a selective poisonous necrotoxic action for the skin of rabbits. The toxin was found to be thermolabile, being completely destroyed when heated to 55° for 1 hour. She recognized the resemblance of this material to leukocidin, but in a later study concluded that the necrotoxic action of the filtrate appears to be due to a different constituent from either the hemotoxic or the leukocidic one.[23] Burnet, on the other hand, is of the opinion that the various manifestations of staphylococcus exotoxin are due to a single antigenic substance. The leukocidin of *Staph. aureus*, according to this investigator, is identical with Parker's skin toxin.[24]

Dr. Weld (née Parker) kindly supplied me with samples of her necrotoxic staphylococcus filtrate. This material injected into the skin of rabbits causes a pronounced edematous reaction. Dye introduced into such an inflamed area is fixed *in situ* and fails to diffuse to the tributary lymphatics. This same material heated for 1 hour at about 58° C. is rendered completely innocuous; *i. e.*, as far as the fixation of a vital dye is concerned.

Berkefeld filtrates of staphylococci which induce prompt cutaneous "walling-off" were tested *in vitro* on tissue cultures of guinea pig mesenteric lymph nodes. Direct examination and microscopic sections of the explants several days later showed relatively few normal cells toward the center of the tissue. There was hardly any migration of cells, and these had for the most part pycnotic and shrunken nuclei. Some cells showed nuclei disintegrated into intensely stained granular material scattered throughout the cytoplasm. The heated or inactivated staphylococcus filtrate, on the other hand, revealed no such injurious effects on the cells of explants. The leukocytes, primarily mononuclear phagocytes, showed normal migration at the periphery of the explants. These cells appeared perfectly normal in regard to their staining property and morphology.

S. aureus filtrate in contact with granular leukocytes obtained from an exudate caused these cells to become swollen and vacuolated. Supravital smears revealed these leukocytes as rounded, immobile cells with little staining of the granules. Evidence was also obtained that the total leukocyte count is lowered when this bacterial filtrate is maintained for some time in contact with an inflammatory exudate. Similar results were obtained by subjecting cells from the lymph of rabbits to unheated and heated filtrates of *S. aureus*. In conclusion these observations strongly suggest that the active principle in the filtrate of *S. aureus* which causes early lymphatic blockage is somewhat similar to, if not identical with leukocidin.

A number of authors including Much,[25] Gratia,[26] and Gengou,[27] have shown that *S. aureus* and its exotoxin are capable of causing

oxalated blood to clot. This, according to Gratia, is due to a thermostable substance which he calls *staphylocoagulase*.[26] Recent studies in collaboration with Mr. H. Walston have demonstrated that evidently "staphylocoagulase" plays no significant rôle in inducing the prompt fixation of trypan blue in the skin of rabbits treated with *S. aureus*. By treating the filtrate of this organism with glacial acetic acid, *staphylocoagulase* can be separated from the principle that induces fixation. The isolated "staphylocoagulase" produces clotting of citrated plasma in the test tube up to a dilution of 1 in 320 of the resuspended precipitate. And yet this material, when injected intracutaneously, although it is absorbed from the skin by lymphatics as indicated by the mild inflammatory cellular reaction in the regional lymph nodes, fails to exert a sufficiently powerful local reaction to obstruct lymphatic drainage by the formation of a fibrinous barrier. Trypan blue diffuses readily from the site of its cutaneous inoculation and the tributary lymphatics are found unoccluded. This indicates that "staphylocoagulase" evidently plays no rôle in inducing mechanical obstruction to lymph flow.* The latter is primarily referable to the powerfully necrotizing action *per se* of the staphylococcus microörganism and of its soluble toxin.

The filtrates of hemolytic streptococci and of Type I pneumococcus are utterly unable to induce any localizing response. The dye penetrates from such inflamed areas to the regional lymphatics even as late as 50 hours following the inoculation of streptococcal filtrates (Tables 3 and 4, Figs. 3 and 4). The filtrates of these latter microörganisms are evidently entirely innocuous.

TABLE 3.—RETENTION OF TRYPAN BLUE AT SITE OF INFLAMMATION INDUCED BY FILTRATE OF PNEUMOCOCCUS TYPE I.

Rabbit No.	Interval between injection of irritant and that of dye.	Total duration of inflammation.	Presence of dye on inflamed side.		Presence of dye on normal side.	
			Lymph of efferent lymphatic.	Lymph node.	Lymph of efferent lymphatic.	Lymph node.
	Hrs. Mins.	*Hrs. Mins.*				
8–77	18.55	23.25	+	+	+	+
8–72	19.04	21.17	Trace	+	0	Faint trace
9–71	23.50	25.45	+	+	+	+
9–86	23.52	25.58	++	++	++	++
8–78	24.00	26.50	++	++	+	++
9–72	24.16	26.16	++	+	+	++
8–80	27.30	29.50	+	++	++	+

* Additional evidence corroborating this conclusion was obtained from the filtrate of a strain of *S. aureus* which failed to elicit the clotting reaction *in vitro* (*i. e.*, staphylocoagulase was evidently absent); and yet, when introduced into the tissues of a rabbit, the filtrate produced an inflammatory reaction with perfectly good fixation of trypan blue.

TABLE 4.—RETENTION OF TRYPAN BLUE AT SITE OF INFLAMMATION INDUCED BY FILTRATE OF STREPTOCOCCUS HEMOLYTICUS.

Rabbit No.	Interval between injection of irritant and that of dye.	Total duration of inflammation.	Presence of dye on inflamed side.		Presence of dye on normal side.	
			Lymph of efferent lymphatic.	Lymph node.	Lymph of efferent lymphatic.	Lymph node.
	Hrs. Mins.	*Hrs. Mins.*				
8–86	43.15	46.21	+++	++	++	+++
8–81.	43.42	46.58	+	++	+	++
9–32	46.18	48.45	+++	+++	++	+++
9–81*	46.29	48.43	+	+	+	+
9–76*	46.50	49.12	++	++	+	++
8–37	49.55	52.35	++	++	+++	+
X	49.55	52.50	++	++	+	++

* Filtrate from culture of strain K-158A, extremely virulent to rabbits; other rabbits injected with filtrate of S–23, Lancefield strain.

The production of leukocidin by either pneumococci or streptococci has been studied by a number of investigators.[28,29,30] Little is known concerning the respective chemical properties and potency of these substances. It is, therefore, conceivable that a highly effective staphylococcus leukocidin may be capable of inducing lymphatic blockage as well as death of cells. On the other hand, with the media employed, the toxins of streptococci and pneumococci, while unable to produce lymphatic blockage may, nevertheless, be sufficiently potent to affect leukocytes.

Recent unpublished studies have clearly demonstrated that the local inflammatory reaction, by determining the degree of invasiveness, is an important factor in immunity.[31] The resistance of the host infected with a virulent microörganism represents the resultant of a number of factors, including among others, the invasiveness and the virulence of the bacteria. The invasive property of a microorganism has often been taken as a criterion of its virulence and *vice versa*.[34] Some bacteriologists have, however, recognized that virulence and invasiveness are different properties which are not to be confused and the terms are therefore not to be employed synonymously.[35]

The factor of invasiveness may be studied as a separate variable by a number of experimental procedures; for example, by interfering with the dissemination of a given virulent microörganism from its site of cutaneous inoculation. This end was attained by the superimposed injection of an inflammatory irritant that causes prompt "walling-off." Such manipulation may delay the dissemination of the virulent microörganism, and even in some cases, apparently allow sufficient time for the local inflammatory reaction to dispose of it in large part. In this way the full effect of virulence, as mani-

fested by massive blood stream invasion and subsequent death, may be delayed, and, in a few cases, even aborted. Nevertheless, there was no indication from these observations that the virulence or the toxic property *per se*, of the pathogenic microörganism had been in any way altered by delaying its invasiveness.[31]

The experiments were set up somewhat as follows: White rabbits were inoculated intracutaneously with varying dosages of a virulent strain of pneumococcus, Type III. This was immediately followed by the introduction of a broth culture of *S. aureus* into the same skin area. It is to be remembered that the latter organism causes rapid "walling-off" of its area of inoculation. When aleuronat or turpentine was employed as the superimposed irritant, similar results were observed as with staphylococci. Control animals received an identical inoculation with virulent pneumococci upon which was superimposed sterile broth, 0.5% saline, or water. None of the latter substances induce lymphatic blockage. All experimental rabbits survived longer than the controls. Two out of 12 animals survived the combined inoculations of virulent pneumococci and staphylococci for over a month. At that time, although both animals were well, one of them was sacrificed. The controls of these two rabbits survived 5 days and 3 days respectively. By comparing and correlating the fixation of a dye at the site of the combined bacterial inoculation with histological findings, it was shown that the increase in survival time of experimental rabbits was entirely referable to the effect of the staphylococcus organism which, by inducing mechanical obstruction in the form of coagulated plasma and fibrinous thrombi in lymphatics, delayed the normal invasiveness of the virulent pneumococci. Blood cultures fully confirmed this interpretation. Whereas 2 or 3 hours following the inoculation of pneumococci in the skin of control rabbits, these organisms were recovered from the blood stream, in the case of experimental animals the virulent organisms were able to penetrate into the circulation not before 13 to 19 hours subsequent to their inoculation. The virulence of the pneumococci was in no way changed by the experimental manipulation. The recovery of pneumococci from the site of skin inoculation of an experimental rabbit injected into a normal animal induced massive infection followed by death several days later. The organisms recovered from the blood of such an animal revealed capsulated pneumococci.

These observations clearly indicate the rôle of the inflammatory reaction in regulating the rapidity of invasiveness of a microörganism and therefore the significance of this factor in grading the immunity or resistance of the host, but in no way does the rate of dissemination alter the virulence *per se* of the bacteria which still remains a most important factor in evaluating resistance. Virulence and invasiveness are therefore regarded as two separate variables in studying problems of immunity.

Conclusion. I have called your attention to the dynamics of the inflammatory reaction in its relation to immunity. Powerfully necrotizing irritants produce as a result of an increase in capillary permeability and of lymphatic damage, an extremely prompt reaction, perhaps best termed *fixation*. By this process, the area of injury is mechanically circumscribed and the dissemination of the irritant is prevented. *S. aureus* is an example of such a bacterial irritant.[12] Aleuronat is a chemical irritant of similar potency.[1] Mild irritants, on the other hand, produce only a delayed reaction, thus allowing relatively free penetration of the irritant into the circulation for a considerable interval of time. Occlusion of the draining lymphatics in such instances often takes place as late as two days subsequently to the inoculation of the irritant. Hemolytic streptococci exemplify this type of irritant. Another instance has been recently demonstrated by McMaster and Hudack[32] who showed that up to 48 hours following a mere skin incision or local burn, lymph drainage is adequate. Subsequently lymphatics failed to convey effectively materials contained in them. The intensity of fixation is found frequently to be parallel to the extent of inflammatory edema. This would suggest that the local swelling is at least in part the result of blockage to normal lymphatic drainage which is thus unable to cope adequately with the excess outpouring of plasma from the capillaries at the site of inflammation.

In relatively large suppurating or acutely inflamed areas the reaction of fixation may occur as early as 30 minutes after the injection of an irritant. This prompt response allows a definite interval of time for the relatively sluggish leukocytes to assemble at the site of inflammation for the purpose of phagocytosis. The neutrophils appear first, to be displaced subsequently by the macrophages. This cytological sequence, as recently demonstrated, is evidently conditioned by changes in the local hydrogen-ion concentration. With the developing local acidosis at the site of an acute inflammation, the predominating cell of the exudate shifts from the neutrophil to the mononuclear phagocytic type.[33] It is conceivable that the mechanism of suppuration is closely associated, perhaps through an activation of autolytic tissue enzymes, with the local increase in the hydrogen-ion concentration of an inflamed area. Studies are now in progress in an attempt to clarify this problem.

The reaction of *fixation* by mechanically circumscribing the irritant in the earliest phase of the acute inflammatory reaction, plays a definite rôle in immunity, for it protects the organism as a whole at the expense of local injury. The reason for the disastrous effects resulting from untimely surgical interference with such an effective inflammatory barrier, as described above, and which is encountered, for example, in the staphylococcus boil or the anthrax carbuncle, is quite obvious and needs no particular emphasis in view of the foregoing discussion.

REFERENCES.

1. Menkin, V.: J. Exp. Med., **50**, 171, 1929.
2. Menkin, V., and Menkin, M. F.: Ibid., **51**, 285, 1930.
3. Menkin, V.: Ibid., **53**, 647, 1931.
4. Menkin, V.: Ibid., **52**, 201, 1930.
5. Auer, J.: Ibid., **32**, 427, 1920.
6. Shwartzman, G.: Ibid., **48**, 247, 1928.
7. Menkin, V.: Arch. Path., **12**, 802, 1931.
8. Sickles, G. M.: J. Immunol., **20**, 169, 1931.
9. Karsner, H. T., and Moritz, A. R.: J. Exp. Med., **60**, 37, 1934.
10. Freund, J.: Ibid., p. 661.
11. Shwartzman, G.: Ibid., **61**, 383, 1935.
12. Menkin, V.: Ibid., **57**, 977, 1933.
13. Menkin, V.: Ibid., **56**, 157, 1932.
14. Opie, E. L.: Tubercle, **7**, 23, 1925.
15. Rich, A. R., and McKee, C. M.: Johns Hopkins Hosp. Bull., **54**, 277, 1934.
16. Menkin, V.: J. Exp. Med., **53**, 171, 1931.
17. Menkin, V.: Proc. Soc. Exp. Biol. and Med., **32**, 162, 1934.
18. Tillett, W. S., and Garner, R. L.: J. Exp. Med., **58**, 485, 1933.
19. Dennis, E. W., and Berberian, D.: Ibid., **60**, 581, 1934.
20. Dennis, E. W.: Personal Communication, 1935.
21. Denys, J., and Van de Velde, H.: La Cellule, **11**, 359, 1895.
22. Parker, J. T.: J. Exp. Med., **40**, 761, 1924.
23. Weld, J. T. P., and Gunther, A.: Ibid., **54**, 315, 1931.
24. Burnet, F. M.: J. Path. and Bact., **32**, 717, 1929.
25. Much, H.: Biochem. Ztschr., **14**, 143, 1908.
26. Gratia, A.: Compt. Rend. Soc. de biol., **83**, 584, 1920.
27. Gengou, O.: Ann. de l'Inst. Pasteur, **51**, 14, 1933.
28. Gay, F. P., and Oram, F.: J. Immunol., **25**, 501, 1933.
29. Oram, F.: Ibid., **26**, 233, 1934.
30. Evans, A. C.: Pub. Health Rep., **46**, 2539, 1931.
31. Menkin, V.: 1935 (unpublished studies).
32. McMaster, P. D., and Hudack, S. S.: J. Exp. Med., **60**, 479, 1934.
33. Menkin, V.: Am. J. Path., **10**, 193, 1934.
34. Zinsser, H.: Resistance to Infectious Diseases, 4th ed., New York, Macmillan Company, 1931.
35. Topley, W. W. C.: Outline of Immunity, Baltimore, William Wood & Co., 1933.

(Titles have been omitted for sake of brevity.)

VARIATIONS IN THE GASTRIC MUCOSA IN PERNICIOUS ANEMIA: GASTROSCOPIC, SURGICAL AND ROENTGENOLOGIC OBSERVATIONS.

By Chester M. Jones, M.D.,

ASSISTANT PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL; PHYSICIAN, MASSACHUSETTS GENERAL HOSPITAL,

E. B. Benedict, M.D.,

ASSISTANT IN SURGERY, HARVARD MEDICAL SCHOOL AND MASSACHUSETTS GENERAL HOSPITAL,

AND

A. O. Hampton, M.D.,

INSTRUCTOR IN ROENTGENOLOGY, HARVARD MEDICAL SCHOOL; ASSISTANT ROENTGENOLOGIST, MASSACHUSETTS GENERAL HOSPITAL,

BOSTON.

(From the Massachusetts General Hospital.)

Since the early studies of Fenwick,[1] Cahn and von Mering,[2] and the subsequent observations of Faber and Bloch,[3] it has been recognized that there are apparently histologic changes in the gastric

mucosa which are invariably associated with the disease, pernicious anemia. These changes, first described in detail by Faber and Bloch, consist in a diffuse inflammatory process leading to the destruction and atrophy of the gastric glands, most striking in the cardia and decreasing in severity toward the pyloric end of the stomach. Achylia, an almost invariable accompaniment of pernicious anemia, is also frequently to be found in the conditions known as atrophic and hypertrophic gastritis. Clinical studies such as those of Hurst[4] and Miller[5] have but served to emphasize the importance of the association between abnormalities of gastric secretion and the presence of a local inflammatory process showing at times hypertrophy and at other times atrophy of the gastric mucosa, and usually designated as chronic gastritis. According to Faber[6] secretory failure probably exists long before there are any marked changes in the gastric mucosa and submucosa indicative of glandular atrophy and characteristic of any chronic inflammatory process.

In cases of pernicious anemia it has been shown repeatedly, as in the reports of Hurst and others, that even after successful liver therapy there is rarely any change in the accompanying anacidity. Usually such observers have considered that the gastritis with its associated secretory changes represents a primary rather than a secondary condition and persists despite any successful treatment of the clinical syndrome known as pernicious anemia. This is also suggested by the studies of Castle,[7] which demonstrated a defective and usually completely absent secretion of the intrinsic factor in gastric juice necessary for normal maturation of the red cells. The histologic studies of Faber and others have been supplemented by direct gastroscopic observations by Henning,[8] Schindler,[9] Benedict[10] and others. All of these observers agree that in pernicious anemia there exists an atrophy of the gastric mucosa as an invariable finding. A quotation from Henning's recent monograph[8] on inflammation of the stomach, which may be used for comparison with the observations to be reported, is given: "I have seen diffuse atrophy of the mucous membrane in all cases of pernicious anemia examined up to the present time, in many cases of complete achylia and carcinoma of the stomach and also in many resected stomachs. The picture of complete atrophy is extraordinarily impressive. The color of the mucous membrane is grayish yellow to grayish green. (The color of normal gastric mucous membrane is red.)* This color tone may be striking only when the stomach is entirely unfolded by marked inflation. By this method even normal or even delicate folds are so perfectly stretched that as a rule they appear entirely smooth or even finely granular. As a further characteristic one notices a strikingly distinct appearance of the coarser and even the finest bloodvessels. The larger bloodvessels arch their course

* Authors' note.

upward along the thin mucous membrane. Since, as a rule, it occurs in small stomachs of the steer horn type there exists a good possibility for observing it also at the pylorus. . . .* One clearly recognizes in the endoscopic photograph the dark appearing vessels in the bright mucous membranes. In the microphotograph of the histological specimen one observes the characteristic disappearance of gastric glands, complete atrophy of specific glands, goblet cell metaplasia and cellular infiltration of the interstitial tissues."

Henning believes that "the sharp outline of the vessels and their distinct arching over in a brilliant mucous membrane of grayish yellow color is decisive" as a diagnostic criterion of atrophic gastritis. He thinks that such a finding is invariably seen in pernicious anemia.

It is important to point out that all the observations noted above have been made on patients suffering from a typical relapse of pernicious anemia. With the exception of studies on gastric secretion, no observations on the stomach itself have been made during remissions following successful treatment of the disease. It is the purpose of this communication to describe the gastroscopic, roentgenologic and other changes occurring in patients suffering from pernicious anemia during a typical relapse of the disease and subsequent observations made during a typical remission. Such observations, although few in number, we believe to be of sufficient importance to warrant reporting in detail, with the hope that they may further stimulate the study of what must be considered as fundamental variations in gastric physiology.

Clinical Material.—The patients were typical cases of pernicious anemia as proved by all of the usual diagnostic criteria. Patient 1 has been under continuous observation since 1917. The 4 remaining patients have been followed by us at this hospital over periods ranging from 1 to 8 years. All 5 of the patients gave typical responses to liver therapy. Gastroscopic examinations were carried out with the flexible Schindler gastroscope and roentgenologic examinations were made using the compression technique (Berg[11]) for the demonstration of the mucosal markings of the stomach. In 3 instances examinations of the stomach were made during a typical relapse and, in addition, subsequent examinations were made at or near the height of a remission. The gastroscopist and roentgenologist both paid particular attention to the prominence, thickening and tortuosity of the gastric rugæ, or to their absence. In 2 instances direct observation of the stomach at operation replaced the initial gastroscopic examination.

Cases. Patient 1, a white man, aged 58, with a negative past history, was first bothered by a sore tongue in 1917, the symptoms persisting for 2 years. In 1919 he entered this hospital with a typical picture of pernicious

* A colored plate showing the gastroscopic appearance of an atrophic stomach can be found in Henning's monograph.

anemia. There had been epigastric pain for the preceding year and the patient had lost 14 pounds in weight.

Physical Examination. Nothing abnormal was noted with the exception of sallow pallor and a smooth, red, sore-looking tongue.

Laboratory Examinations. Negative except for blood and gastric analysis. The red count was 2,640,000 and the blood smear showed the typical changes characteristic of pernicious anemia. There was marked macrocytosis with striking inequality in size and shape of the red cells which were well filled with hemoglobin. The blood platelets were somewhat diminished. A gastric analysis after an Ewald test meal showed no free hydrochloric acid in any of the specimens collected.

Repeated Roentgen rays taken at this time showed suggestive changes in the antrum of the stomach on 2 occasions, although a third examination showed no evidence of disease.

The patient was discharged unrelieved with a diagnosis of pernicious anemia.

A spontaneous remission occurred and the patient remained in good health until 1922, at which time there was a typical relapse with sore tongue, loss of weight, and anemia. At this time the patient was advised to eat large quantities of red meat, which he did for a period of about 2 months. A sharp, spontaneous remission again occurred, due probably to the large quantities of meat ingested and the fact, noted later, that presumably he had a small amount of Castle's intrinsic factor in his gastric secretion. Since the advent of liver therapy the patient has taken liver or liver extract at frequent intervals, maintaining the normal level of his blood without difficulty without the recurrence of the stomatitis, paresthesias, or other symptoms, until 1934 when a slight relapse occurred which was relieved by the regular addition of liver to his diet for a short time.

It is of some interest that a second gastric analysis performed with histamin, in 1925, showed a maximum free titratable acidity of 25 cc. tenth-normal acid at the end of 1 hour. It is probable, as already suggested, that the presence of moderate amounts of free hydrochloric acid was associated with at least minimal amounts of Castle's intrinsic substance. Such a fact would explain the relative ease with which the patient maintained himself free of symptoms of the disease with only moderate therapeutic measures. Because of the finding of free hydrochloric acid after histamin the case was reviewed, but it was the opinion of Dr. George Minot as well as ourselves that there was no reason to doubt the diagnosis of pernicious anemia.

During the past 3 or 4 years there has been mild, indefinite epigastric distress and belching, usually associated with fatigue or indiscretions in diet. The day before his second admission on June 29, 1934, the patient felt weak, had generalized abdominal distress and suddenly vomited a large mouthful of free blood. In the next 24 hours there were two more attacks of hematemesis and a tarry stool was passed.

Physical examination on this admission was negative except for pallor and a tongue which was slightly smooth at the edges.

Laboratory Data. Urine negative. Red count, 3,040,000. Hemoglobin, 65%. A blood smear showed slight achromia of the red cells with moderate variation in size and shape. Stool examinations showed evidences of occult blood.

The admission diagnosis was pernicious anemia and probable polyposis.

Ten days after admission all signs of bleeding had subsided. Roentgen rays of the stomach taken at that time showed a small hiatus hernia and apparently a polyp of the antrum.

Gastroscopy showed a moderately pale mucous membrane but not characteristic of complete atrophy of the stomach. No bloodvessels could

be seen. Gastric rugæ were absent. Only glimpses were obtained of the antrum where there appeared to be a thickening of the mucous membrane which might have been a polyp.

Because it was felt that the hemorrhage was due to a polyp of the stomach, surgery was decided upon and operation was performed 1 month after admission. On the lesser curvature a hard nodule was felt which, on resection, proved to be a lymph node. Frozen section showed carcinomatous involvement of a very malignant nature. The stomach was opened about 3 inches from the pylorus and on exploration of the greater curvature a small carcinoma was found and local resection was performed.

Subsequent examination of the resected stomach and the lymph node showed adenocarcinoma. Sections of the fundus adjacent to the tumor showed dilatation of some of the tubules, but for the most part the gastric tissue appeared normal. There appeared to be no atrophy. The parietal cells were present in normal numbers. In the sections studied there was no evidence of gastritis.

Convalescence was uneventful and since the operation the patient has gained weight and strength and has been symptom-free. He has been working steadily and since November, 1934, his blood has returned to and remained at an absolutely normal level. Gastroscopy performed in March, 1935, showed slight apparent hypertrophy of the gastric mucosa without any evidence of polyps or of metastases. A Roentgen ray examination made at the same time, and again in June, 1935, revealed no evidence of metastases or of gastritis.

The findings in this case are of particular interest when contrasted with those made on the 4 following patients, 3 of whom were examined in a typical relapse as well as during a remission. In this particular instance the gastroscopic and roentgenologic examinations were made to determine the cause of hematemesis during a period in which the patient had no symptoms of pernicious anemia.

Patient 2, a white man, aged 57, with an irrelevant past history, 8 years before admission began to notice subxiphoid distress immediately after meals associated with very irregular eating habits. This was relieved by induced vomiting. A return to regular eating habits relieved his symptoms for the most part with the exception of occasional attacks of mild indigestion always associated with fatigue or irregularity in eating. One year before admission the patient noticed easy fatigability culminating in an attack of pain in both axillæ and upper arms, particularly on the left side. He was seen by a consultant who made a diagnosis of probable coronary disease and at the same time noted that he was slightly jaundiced. After 5 weeks in bed the patient had a sudden attack of right upper quadrant pain with an increase in jaundice and residual soreness in the abdomen. A second consultant diagnosed cholelithiasis. Continued rest for the next few months resulted in a clearing of the jaundice, but on resuming some physical activity the patient noticed extreme fatigability, dyspnea and substernal distress on slight exertion. Indigestion and loss of appetite were prominent symptoms for the next 4 months with some nausea and a loss of about 8 pounds. Just before admission he noticed some soreness of his mouth and "canker sores" on his tongue. He was admitted to the hospital for study on September 26, 1934, and an immediate diagnosis of pernicious anemia was made, based on the appearance of the patient and further proved by examination of the blood.

Physical examination showed a sallow, pale individual with slight icterus of the scleræ. The tongue was slightly smooth around the edges. Exam-

ination was otherwise essentially negative except that the liver was easily palpable 6 cm. below the costal margin in the right midclavicular line.

Laboratory Data. Urine and stools negative. Red count, 2,240,000. Hemoglobin, 45% (Tallqvist). The stained smear of the red blood cells was characteristic of pernicious anemia. Gastric analysis with histamin showed complete anacidity.

Roentgen ray examination of the stomach showed what appeared to be several large polyps along the greater curvature and a striking increase in all the gastric rugæ. A radiograph of the gall bladder area showed shadows characteristic of biliary calculi.

An electrocardiogram was normal.

Because of the above findings a diagnosis of pernicious anemia, gastric polypi, with possible carcinomatous degeneration, and cholelithiasis was made. It was felt that the symptoms of coronary disease were fundamentally due to the marked anemia and that operative procedures were justified if the blood could be brought back to normal. Intensive parenteral liver therapy was initiated with a typical response in the reticulocytes which rose to 17.3% in 1 week, and a rise in the red count at the end of 1 month to 4,020,000. The failure to obtain a more satisfactory rise in the red count was due to the fact that there was an interval attack of acute cholecystitis with fever, chill, leukocytosis, increased jaundice and sharply localized tenderness over the gall bladder area. At the end of 1 month it was decided that operation on the gall bladder was necessary, although we had at first hoped to do a gastric resection.

At operation a subacute cholecystitis was found and a thick-walled, ulcerated gall bladder containing many pigmented stones was removed. Because of the condition of the patient it was deemed unwise to attempt a large gastric resection, but the stomach was opened and two large polypoid tumors which had been localized by Roentgen ray were removed with resection of a broad base. The remainder of the stomach was inspected carefully and showed a very dark red mucosa with marked hypertrophy of all the rugæ, which at times were so thickened as to present verrucous enlargements that had the appearance of polypi or tumor masses. The appearance was characteristic of hypertrophic gastritis. Drainage of the gall bladder area was instituted and the abdomen closed. The patient had an uneventful recovery and was discharged from the hospital 1 month after admission with a red count of 4,670,000 and a hemoglobin of 75%. Clinically he was symptom-free and on moderate exertion had no cardiac symptoms whatever.

Microscopic examination of the polypi removed from the stomach showed evidence of active growth. The gland tubules were large and irregular in size and shape. There was no evidence of invasion but it was considered as potentially malignant. A subsequent examination of serial sections of the base showed definite invasion by tumor in the pedicle of the growth below the muscularis mucosa and a diagnosis of adenocarcinoma was made.

Two months after discharge the patient reëntered the hospital for gastroscopy. On physical examination the patient showed a profound change, with a complete absence of pallor and a return to normal weight. The liver which previously had been definitely enlarged was no longer palpable, and the patient stated that he felt better than he had for years and had no digestive disturbances. His red count was 4,770,000. The blood smear showed no sign of abnormality of the red cells.

Gastroscopy showed a mucous membrane of normal color with apparently normal gastric markings. There was no suggestion of atrophy and very questionable hypertrophy of the rugæ. Roentgen ray findings at that time showed much less thickening of the gastric mucosa than had been noted on previous films. The polyp previously described could not be

demonstrated. There was no evidence of recurrence of any carcinomatous process and the appearance was that of an active gastritis.

Four months after the operation the patient had more than regained his lost weight, was working and felt perfectly well. The gastroscopic examination at this time showed a normal color of the mucous membranes with a few bright red areas between the folds and one diffuse area suggesting submucous hemorrhage. The rugæ were present and appeared normal. There was no evidence of recurrence of the tumor or of polypoid formation. The appearance was that of a mild superficial gastritis but did not suggest atrophy. Roentgen ray findings at this time showed very little change from the previous examination. There was no evidence of recurrence of malignancy.

When last seen, 9 months after the operation, the patient was still in excellent health and 8 pounds heavier than he had ever been.

Patient 3, a white man, aged 62, past history irrelevant, 6 months before admission noticed weakness and shortness of breath on exertion with swelling of his ankles at the end of the day, pallor and questionable jaundice. During the latter part of his present illness he developed numbness and tingling of his hands and toes. Anorexia, constipation, nausea and vomiting were important symptoms without loss of weight. He was told that he was anemic and was treated with iron with temporary relief of symptoms except for the paresthesias which persisted. One month before admission all his symptoms returned. He was seen in the Outpatient Department where Roentgen rays were taken and a blood examination was done. A diagnosis of pernicious anemia was made. The Roentgen ray examination showed an irregular filling defect with evidence of crater formation involving the lower half of the stomach. The findings were thought to be those of carcinoma involving the lower half of the stomach.

Physical Examination. On admission the patient showed a striking sallow pallor, otherwise there were no physical findings of importance.

Laboratory Data. Urine and stool examinations were negative. Red count, 1,380,000. Hemoglobin, 45% (Tallqvist). The stained smear of the red cells was characteristic of pernicious anemia. Gastric analysis with histamin showed complete anacidity.

Reëxamination of the stomach by Roentgen ray confirmed the previous findings and showed a large defect in the pyloric end of the stomach. Gastroscopy showed a very pale, thin mucous membrane throughout the entire stomach. Numerous small bloodvessels could be very well seen. Normal rugæ were almost entirely absent. On the lesser curvature and posterior wall in the antrum of the stomach there was a rounded elevated red lesion, smooth in contour, attached by a broad base. The lesion was about 7 to 8 cm. in diameter. It was thought that the appearance of the mucosa was absolutely typical of the atrophy seen in pernicious anemia in a relapse and it was also felt that probably the lesion was a benign polyp, although there was a definite chance of early malignant degeneration.

It was decided to resort to surgery as soon as the patient's condition permitted and after 2 transfusions operation was performed. The tumor was easily palpated and on opening the stomach a long tongue-like polyp about 6 inches in length and ulcerated in two places was seen on the posterior wall about one-third of the way up from the pylorus. This was excised with a wide margin around the base. Microscopic examination of the tumor showed no evidence of malignancy and it was diagnosed as a benign gastric polyp. Examination of the surrounding mucosa showed some exaggeration of depth and tortuosity of the superficial portion of the antral glands, otherwise they were not remarkable. The cells lining the deepest portion of the pyloric glands were low and the lumina were large.

The patient had an uneventful convalescence and on discharge, 7 weeks after admission, his red count had risen to a level of 3,900,000 with a hemoglobin of 70% on adequate liver therapy.

He was readmitted to the hospital 5 months later for further treatment of his pernicious anemia, intensive treatment having been discontinued through a misunderstanding on the part of the patient. He had been perfectly well up to 1 month before admission, when his symptoms of weakness and shortness of breath returned. On admission his red count was 1,700,000 with a hemoglobin of 45%.

Gastroscopic examination was repeated and at this time the mucosa presented a very different appearance from that of the previous examination. The color was moderately pale in some areas, in other areas the color was approximately normal, the whole appearance being that of a rather blotchy dark and light pink surface. Rugæ were present along the greater curvature and were somewhat irregular but appeared nearly normal in size. Near the antrum there was a pseudopolypoid arrangement. The gastroscopist felt that there was a chronic gastritis present in a transitional stage from the previously described atrophic type. He felt it was tending towards the verrucous or hypertrophic type. Intensive liver therapy was instituted and there was prompt response showing a rise in the red cells to 2,500,000 and the hemoglobin to 60%.

A subsequent gastroscopy 2 months later showed a mucous membrane absolutely normal in color with no evidence of atrophy. There appeared to be a very superficial gastritis without obvious evidence of hypertrophy. The red count at this time was 3,660,000 with a hemoglobin of 65 to 70%.

Patient 4, a white woman, aged 70, past history irrelevant, first noted easy fatigability in 1925 with associated palpitation on exertion. One year later there was mild indigestion with anorexia and a loss of 25 pounds in weight in the following 2 years, at the end of which time she was admitted to the hospital. There was some intermittent soreness of the tongue. On admission her presenting symptom was diarrhea of 10 days' duration without blood or cramps.

Physical Examination. Essentially negative except for pallor and loss of weight.

Laboratory Data. Urine and stool examinations negative. Red blood cells, 2,000,000. Hemoglobin, 60%. Stained smear of the red blood cells was consistent with pernicious anemia with moderate macrocytosis. Gastric analysis showed frank blood in all specimens. There was no free hydrochloric acid after an Ewald test meal and only 5 cc. of total acid as a maximum secretion.

Roentgen ray examination showed well defined mottling involving the pyloric end of the stomach and the duodenal cap. These findings were interpreted as indicative of polyposis of the stomach and first portion of the duodenum.

A diagnosis of pernicious anemia and gastric polyposis was made and the patient was treated with liver by mouth with a rise in the red count to 3,400,000 in 4 weeks. The patient was then discharged from the hospital on a dosage of 300 gm. of whole liver by mouth daily and showed gradual but steady improvement. Her appetite remained only fair, however, and the diarrhea was not entirely controlled. In addition there were several attacks of acute "indigestion" with some epigastric pain lasting for several hours without chills, fever or jaundice.

She was admitted to the hospital again after a period of 6 weeks, at which time the physical examination was the same as on the first admission. The red count was 4,800,000, hemoglobin, 75%, and a practically normal blood smear. Repetition of the gastric analysis again showed gross blood and no free hydrochloric acid after a test meal, although there was a max-

imum total acidity at this time of 24 cc. tenth-normal acid. Stool examinations gave a strong test of occult blood.

A second Roentgen ray examination was interpreted as confirming the previous diagnosis of polyposis of the pyloric end of the stomach.

The patient was discharged without additional treatment and was followed in the Outpatient Department for the next 4 months, at the end of which time she entered the hospital for the purpose of operation. During this 4-month period she was bothered by a good deal of gas and distention accompanied by a burning pain of moderate severity occurring 2 hours after meals and relieved by cold water. Diarrhea of a moderate severity had been an intermittent symptom.

Physical examination at this time revealed an irregular tender mass under the right costal margin which was thought to be the liver.

The blood examination showed a red count of 5,500,000 with a hemoglobin of 90%. The stools again showed evidence of occult bleeding and the gastric analysis remained unchanged.

Operation was decided upon and was performed at this time. The stomach was opened by a longitudinal incision and appeared everywhere to be covered with small polyps, the largest of these were about 3 inches in diameter. In addition the rugæ in several places seemed to be thickened as if edematous. The whole area from the pylorus to the cardia was "red and inflamed." A section of the stomach was taken for microscopic examination but it was decided that nothing short of a complete gastrectomy would offer a solution and this was deemed inadvisable. Accordingly, no further surgical procedure was performed. The biopsy showed lymphoid cell infiltration and areas of infiltration in the mucous membrane and wall. A diagnosis of a chronic inflammatory process was made.

Four years later the patient came to the Outpatient Department in response to a letter. She said she had been very much better since the operation. There had been no loss of weight and the only symptoms were those of slight epigastric distress after eating without nausea or vomiting. She was working full time and was on a liberal unrestricted diet. In addition she had been taking dilute hydrochloric acid and 2 pounds of raw liver a week. At this time the stomach was examined with small amounts of barium and no constant filling defects could be seen which could be interpreted as polyps. There were a few 0.5 cm. shadows between the greater and lesser curvatures which possibly could be interpreted as polyps. There were no defects in contour or interference with peristaltic movements and no disturbance of gastric rugæ. The note was made that this Roentgen ray examination showed definite improvement over the findings of 5 years before. Another Roentgen ray was taken a month later with more careful technique. The report was that the only definite variation from the normal was marked thickening of the gastric rugæ. It was thought that the deformity was quite typical of hypertrophic gastritis.

Two years later the patient was seen again and said that she felt well and strong. Treatment had been the same throughout this 2-year period with the blood remaining at a normal level. Roentgen rays taken of the stomach by compression technique at this time showed no positive variation from normal except for some possible thickening of the mucosa about the pyloric valve on the duodenal side.

A gastroscopy was done at this time. The rugæ appeared rather large and slightly tortuous at first but with inflation they almost disappeared and the mucous membrane appeared smooth and glistening. The color was approximately normal. No bloodvessels were seen and there was not the pallor seen in advanced pernicious anemia. No ulcerations, erosions or excrescences were noted. The findings were thought to be those of a nearly normal stomach.

Patient 5, a white man, aged 46, with a past history essentially negative except for dental sepsis, for 6 months had noted anorexia, slight nausea before eating, and for 1 month before admission dyspnea on exertion with substernal tightness. At the same time he noted numbness of his hands and legs and marked pallor. There was a loss of 10 pounds during the 6 months.

Physical Examination. There was moderate icterus, marked pallor, dental sepsis and a slight diminution of vibration sense over the right shin. Otherwise the examination was essentially negative.

Laboratory Data. The urine and stool examinations were essentially negative. Examination of the blood showed a red count of 1,270,000 with a hemoglobin of 40%. The smear was characteristic of that seen in pernicious anemia. Gastric analysis showed complete anacidity with histamin.

Roentgen ray examination showed that the gastric rugæ were slightly more prominent than normal.

Gastroscopic examination showed that the mucous membranes were much paler than usual, particularly in the fundus where a network of bloodvessels was seen. In some areas the mucosa was of a fairly normal red color and the entire appearance was that of a rather blotchy white and pink appearance. On the greater curvature near the antrum there was a definite nodular protuberance 2 cm. long. It was thought that the findings were those of an atrophic gastritis with probable pseudopolyposis.

Intensive liver therapy was instituted at once with a gradual rise in the red count so that 3 months later the red count was 4,690,000. The relatively slow rise in the number of red cells was due to the fact that during the course of the treatment several fractions of liver extract that were being used were found to be of relatively low potency. With the rise in the red count all symptoms disappeared.

A second gastroscopic examination was made 2 months after admission. At this time the color of the mucous membrane was practically normal. The mucosa appeared somewhat granular in places, indicating a mild gastritis. On the greater curvature there was a small smooth swelling which did not disappear on inflation and might have been either a true polyp or a pseudopolyp. High up on the posterior wall there was an area of increased redness which appeared to be a submucous hemorrhage. There was no doubt that the appearance of the mucous membrane had improved in a striking fashion since the first examination, and in no sense could be classified at this time as that of an atrophic gastritis.

Discussion. From the preceding observations several facts of interest are to be noted. By comparison with the accepted description of gastric atrophy, as previously given, typical atrophy was noted at gastroscopy in 2 of the 5 cases, Patients 3 and 5, at the first examination, and slight atrophic changes were to be seen in one other, Patient 1. The 2 patients showing marked atrophy were at the time in a typical relapse of the disease with red blood counts under 1.5 million. In the third case, Patient 1, having a red count of 3.6 million, there was very slight evidence of atrophy at the time of gastroscopy. The other 2 patients, when examined with a gastroscope, showed no evidence of an atrophic process, the red counts at the time of this examination were 5.5 and 4 million red cells, respectively. It would seem to follow that gross atrophic changes in pernicious anemia need be expected only in those patients suffering from a typical relapse. That the gross appearance of atrophy may be absent even during the period of relapse is appar-

ently true from the fact that Patient 2 showed an extremely hypertrophied, inflamed stomach at the time of his operation, at which time he was just beginning to show a proper response to liver therapy.

From gastroscopic observations, therefore, it is obvious that, contrary to the generally accepted views, atrophy of the stomach is not an invariable accompaniment of pernicious anemia. Following successful treatment of the anemia by appropriate liver therapy, later gastroscopic examinations showed striking changes in the appearance of the stomach in each instance. In the case of Patients 3 and 5, where previously there had been a characteristic appearance of marked gastric atrophy, all suggestion of an atrophic process had disappeared in the course of 5 months and 2 months, respectively. In the place of a pale, smooth mucosa with easily visible bloodvessels and an absence of the rugæ there was a complete return to normal color, the rugæ appeared normal, no bloodvessels could be distinguished, and the appearance was that of a mild superficial gastritis. In Patient 1 the changes were less striking, inasmuch as the original appearance, even after the pernicious anemia had been present for years, was that of only slight or questionable atrophy, but they were of the same nature as those just described. This was not surprising in view of the fact that at the first gastroscopic examination Patient 1 was not in a relapse but was suffering from a post-hemorrhagic anemia. In those patients showing no gross evidence of atrophy at the first examination there was also a marked change following a course of specific therapy of the previous anemia. In both Patient 2 and Patient 4 the initial observations were those of marked hypertrophic gastritis. Following liver therapy there was a gradual but striking return to a normal appearance.

The operative findings in 3 of the 4 patients, Patients 1, 2 and 4, who came to surgery were similar. Unfortunately no adequate description of the stomach was given after operation in Patient 3. On inspection of the stomach in the 3 cases noted there was no gross evidence of atrophy, but the appearance was rather one of a diffuse inflammatory process with marked hypertrophy of the rugæ. In 2 cases, Patients 2 and 4, the rugæ were so thickened it was impossible to determine whether polyps were present or merely a thickening of the mucosa (pseudopolyps). None of the 3 patients was in a severe relapse when operated upon, the red counts being 3.6, 5.5 and 4 millions, respectively. In the case of Patient 1, the lowered red count was due fundamentally to a recent gastric hemorrhage from a polypoid tumor in the stomach.

Microscopic examination of gastric tissue removed at operation confirmed the observations already noted. The pieces of tissue examined showed no evidence of an atrophic process in any of the cases, although there was a marked inflammatory process with

lymphoid cell infiltration and hemorrhage in the mucosa and submucosa in two instances.

The Roentgen ray examinations constituted an interesting check on our other observations but gave much less accurate information than that obtained either by gastroscopy or by direct examination at operation. In general it can be said that the chief value derived from such examinations was that of noting progress in a given case. This was shown in the set of observations obtained in Patient 4. In 1927 and 1928 three observations were made, all showing marked hypertrophy of the gastric rugæ which was interpreted as meaning a diffuse polyposis of the stomach. Examination of the stomach at operation in 1928 apparently confirmed these observations, although microscopic examination of the biopsy specimen revealed only the chronic inflammatory changes present in pseudopolypoid formation. After $5\frac{1}{2}$ years of constant liver therapy, 2 further Roentgen ray studies were made and a year later a final examination was made. At the latter examination there was a change of such a degree that in the final Roentgen ray it was impossible to find any positive variation from the normal except for some apparent thickening of the mucosa on the duodenal side of the pylorus. Gastroscopy performed at the time of the last examination was essentially normal. Associated with these changes there had been a gradual and steady disappearance of all gastric symptoms. The discrepancy between gastroscopic and roentgenologic findings has been noted by others and in making an accurate diagnosis of atrophic or hypertrophic gastritis, polypoid formation and the like, it is undoubtedly true that gastroscopy offers the most valuable diagnostic aid that we have.

It remains to be said that although atrophy was absent in all 5 patients when the anemia was responding to proper treatment, there was present in every case gastroscopic evidence of a definite chronic gastritis.

Repeated examination of the gastric secretion in several of the patients revealed no return of hydrochloric acid where previously achlorhydria had been present. Such a finding was, of course, to be expected and has been discussed frequently by others. According to Faber, in older patients, regardless of the underlying cause, achlorhydria when once established rarely shows any tendency to change, even where there is a complete disappearance of all associated symptoms. He also made the important observation, which is applicable to the cases under discussion, that achlorhydria may be present in the complete absence of any microscopic evidence of gastritis and may be considered as one of the earliest symptoms of the disease in its chronic atrophic form.

In view of the nature of the preceding observations, one cannot escape the conclusion that adequate treatment of pernicious anemia not only permits a proper maturation of red cells but also is asso-

ciated with a subsidence of the inflammatory process in the stomach itself and the disappearance of the atrophic process. This was particularly marked in Patients 3 and 5 in whom there had been striking atrophy of the mucosa at the early examinations made during a relapse, with recovery to an almost normal appearing mucous membrane after as short a period as 2 months of intensive treatment. In the case of Patient 3 a resection of gastric tissue was done 1 month after gastroscopy had been performed and liver therapy had been instituted. At the time of this gastroscopy there was extreme atrophy which corresponded in every way to Henning's description previously quoted. The microscopic appearance of the gastric tissue removed at operation 1 month later showed very little evidence of an atrophic process. There was some exaggeration of the depth and tortuosity of the superficial portions of the antral glands and the cells lining the deepest portions of the pyloric glands were low.

The striking changes between the original observations of extreme atrophy and the subsequent observations showing almost normal gastric mucous membrane were clearly associated with clinical improvement in the patient's condition and a corresponding rise in the red count. This apparent change from a very atrophic mucosa to a normal one might conceivably be the result of an improvement in the anemia with coincident improvement in the local blood supply. It would seem more logical, however, to believe that the changes noted in the gastric mucous membrane were of the same nature as those frequently observed in the tongue. It is a well known clinical fact that the glossitis associated with pernicious anemia, with its more or less complete obliteration of the normal papillæ, undergoes a profound change in many cases following intensive specific therapy. Not infrequently the papillæ return and the smooth appearance of the tongue completely disappears as the remission progresses. It is not at all improbable in our opinion that much of the gastric atrophy noted in pernicious anemia by various observers represents an atrophy of the mucous membranes due fundamentally to a specific deficiency rather than to a chronic gastritis. The rapid return to normal which we have observed may well represent an epithelial change associated with successful treatment of a specific deficiency state rather than the healing of a chronic inflammatory process. One is even tempted to speculate as to the possibility that at times the gastritis associated with pernicious anemia may follow the degenerative changes in the epithelium rather than initiate them. By this statement we do not infer that chronic gastritis may not be a causal factor in certain cases of pernicious anemia. The histories of several of the patients discussed above suggest very definitely that chronic gastric irrita-

tion existed for some time before the development of pernicious anemia.

It is of interest that, as in the cases showing marked atrophy, so in those with striking hypertrophy (Patients 2 and 4) there was a return to a normal appearing mucous membrane after proper treatment. In the case of those patients with hypertrophic changes, the return to normal involved a longer period of time. It is quite probable that, in the presence of a hypertrophic gastritis of long duration, the response to liver therapy involves not only a specific response to the active principle needed in the treatment of pernicious anemia but also a gradual subsidence of a definite chronic gastritis. In any event, there appears to be little room for doubt that the successful treatment of pernicious anemia with the active principle contained in liver may be followed by the subsidence of any underlying gastritis and a disappearance of associated hypertrophic or atrophic changes in the gastric mucous membrane.

Summary. 1. Five cases of pernicious anemia are presented with special reference to the appearance of the stomach before and after successful treatment of the disease. Observations of the stomach were made by gastroscopic and roentgenologic examination, by direct observation at laparotomy and by histologic examination of biopsy material.

2. Evidence is presented which we believe indicates that, contrary to most observers, atrophy of the stomach occurs particularly during a relapse and not as an invariable accompaniment of the disease.

3. Evidences of hypertrophic gastritis have been observed by Roentgen ray during a relapse and also during the early stages of a remission.

4. Following specific therapy of the pernicious anemia, evidences of atrophy and hypertrophy of the stomach have both tended to disappear.

5. We suggest that the change from an appearance of atrophy to that of a normal gastric mucosa frequently represents an epithelial change associated with successful treatment of a specific deficiency state rather than the healing of a chronic inflammatory process.

6. We believe that the apparent return to normal from a grossly hypertrophic condition of the gastric mucous membrane represents a subsidence of a chronic gastritis.

REFERENCES.

1. Fenwick, S.: On Atrophy of the Stomach, London, J. and A. Churchill, 1880.

2. Cahn, A., and von Mering, J.: Die Säuren des gesunden und kranken Magens. Deutsch. Arch. f. klin. Med., **39**, 233, 1886.

3. Faber, K., and Bloch, C. E.: Ueber die pathologischen Veränderungen am Digestionstractus bei der perniciösier Anämie und über die sogenannte Darmatrophie. Ztschr. f. klin. Med., **40**, 98, 1900.

4. Hurst, A. F.: Achlorhydria and Achylia Gastrica, and Their Connection with Addison's Anæmia—Subacute Combined Degeneration Syndrome and Simple (Non-Addisonian) Achlorhydric Anæmia, Quart. J. Med., **1**, 157, 1932.

5. Miller, T. G.: Gastritis in Its Relation to Other Diseases, Am. J. Med. Sci., **186**, 192, 1933.
6. Faber, K.: Gastritis and Its Consequences, Oxford Med. Pub., 1935.
7. Castle, W. B., and Locke, E. A.: Observations on the Etiological Relationship of Achylia Gastrica to Pernicious Anemia, J. Clin. Invest., **6**, 2, 1928.
8. Henning, N.: Die Entzündung des Magens, Barth, Leipzig, 1934.
9. Schindler, R.: Lehrbuch u. Atlas der Gastroskopie, Lehmann, München, 1923.
10. Benedict, E. B.: Chronic Gastritis, a Clinical Discussion Based on Gastroscopic Examination, New England J. Med., **212**, 11, 468, 1935.
11. Berg, H. H.: Röntgenuntersuchungen am Innenrelief des Verdauungskanals, 2d ed., Leipzig, Georg Thieme, 1931.

DISTRIBUTION OF THE ERYTHROCYTE POPULATION IN REGARD TO DIAMETERS AND OSMOTIC RESISTANCE IN SPLENECTOMIZED CASES OF HEMOLYTIC ICTERUS.

A Contribution to an Understanding of the Pathogenesis of the Disease.

By Dr. G. Momigliano-Levi,
and
Dr. A. Bairati,
Turin, Italy.

(From the General Medical Clinic of the University of Turin, Director, Prof. F. Micheli.)

The thesis upheld by Italian authors, and especially by Micheli and Banti, that the spleen holds a central position in the pathogenesis of the primary hemolytic splenomegalies, has been more and more confirmed as our knowledge about this interesting chapter of pathology has become more accurate. Today, therefore, it may be recognized as highly probable that the *primum movens* of such splenomegalic syndromes is hyperhemolysis.* This statement does not exclude by any means the existence of a constitutional diathesis of the bone marrow toward special kinds of pathologic erythropoiesis, a state of affairs which appears only too probable if one bears in mind the strikingly different modes of erythropoiesis in the primary hemolytic splenomegalies and also in other forms of hemolytic anemia, obviously not constitutional, in which the very high percentages of pathologic erythrocytes that are found in the primary forms are far from being attained.

The study of the curves of erythrocyte diameters and of their osmotic resistances, in the period immediately following splenectomy in cases of hemolytic icterus, has shown profound and rapid modifications which we have treated in detail in an article now in press,

* To prevent confusion it should be stated that in many countries the primary defect in hemolytic icterus is thought to lie in an inherited defect of the small, fragile spherocyte. As this article has been translated in our editorial department, the authors should not be held responsible for errors in phraseology.—Editor.

changes which we would like briefly to comment upon here. The behavior of these curves until now has lacked precise description, as the hematologic changes, such as those studied by Gamna, in our clinic, refer to a period distant from the operation. If it is possible, as one of our cases demonstrates, to change the production of microcytes by splenectomy in the direction of normocytic erythropoiesis, and to obtain at the same time an almost normal osmotic resistance, it is difficult not to find therein proof that the bone marrow in these patients is not profoundly and constitutionally compromised as regards erythropoiesis.

It is expedient in cases of hemolytic icterus to admit a potential disposition of the marrow toward the production of red cells with an abnormal structure. Such a disposition might be changed into an actual occurrence when the contingencies, such as are present in hemolytic icterus, push the marrow to a prolonged hyperactivity in compensation for the hemolysis.

Let us pass without further ado to the data of our 2 cases which essentially present the following:

Instead of the monoapical curve representing the individual variations of diameters and osmotic resistance of the erythrocytes before splenectomy, there is substituted after the operation a biapical curve, a fact which demonstrates the existence of a mixed erythrocyte population. The existence of this mixed population may be, but is not always, transient, tending to evolve into a normocytic population with normal resistance. We need not be astonished, therefore, that the measurements taken some time after splenectomy with methods that are less sensitive than ours do not give the same clear indications.

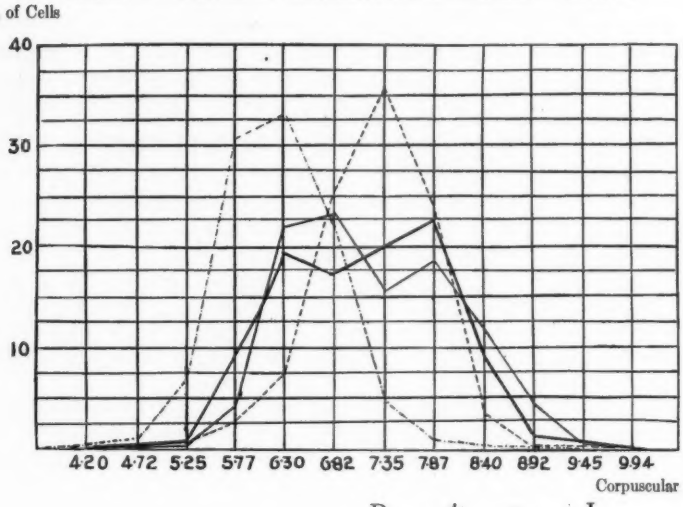
The 2 cases of hemolytic icterus that we have studied after splenectomy* gave the complete syndrome of splenomegaly (extreme in the first case, the spleen weighing about 1 kg.), acholuric icterus (dating from a few days after birth), anemia with a high color index, diminished diameters and globular resistance.

The first case was characterized hematologically (Charts 1 and 2) in the pre-splenectomy period by the fact that the red cells were almost entirely in the form of spheroidal microcytes (93% of the erythrocytes had a diameter less than 7.35 μ), and by the fact

* The erythrocytometric and the reticulocytometric curves were obtained from dry spreads that had been fixed in methyl alcohol, making at least 1000 counts for the erythrocytes and several hundred (generally 300) for the reticulocytes. The measurements were made with an optic system of a micrometric value of 1.05 μ which, for the normal subject, gives an almost symmetrical monoapical erythrocytometric curve, formed by 8 divisions between 5.77 and 9.45 μ and with the following statistical values: D = 3.7; φ = 7.6; σ = 0.57; I = −0.01; and a monoapical reticulocytometric curve formed by 7 divisions between 6.3 and 9.45 μ, with the following statistical values: D = 3.1; φ = 7.7; σ = 0.5 to 0.55; I generally positive.

For the curve of osmotic resistance Hamburger's method was used. This also made use of 8 divisions between the concentrations of 1.4% and 0.7% of $Na_2SO_4 \cdot 10H_2O$, and is monoapical.

CHART 1.—CURVES OF ERYTHROCYTE DIAMETERS. CASE 1.

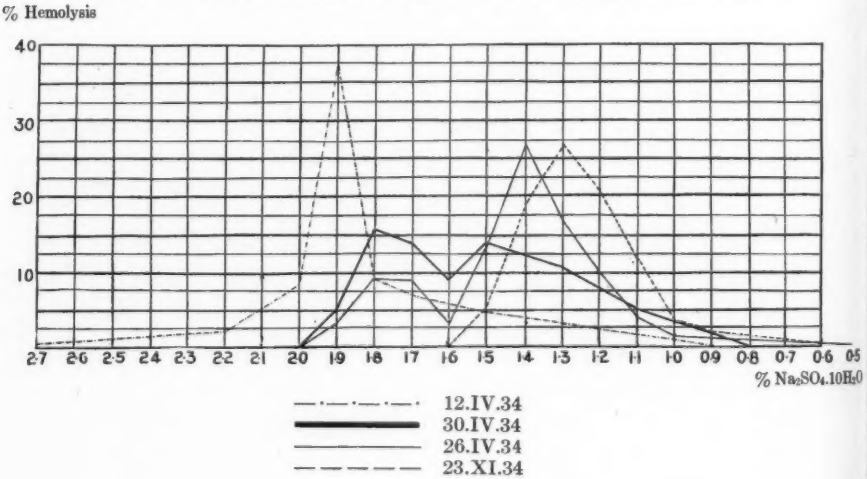


		D	ψ	σ	I
—·—·—·—	12.IV.34	5,77	6,21	0,59	−0,13
———	25.IV.34	5,77	7,20	0,85	+0,1
▬▬▬	30.IV.34	5,25	7,22	0,84	−0,2
— — — — —	23.XI.34	4,72	7,24	0,61	−0,3

Dates.	Hb.	R.B.C., mill. per c.mm.	Color index.	Corpuscular volume, cubic micra.
April 12	68	3.53	0.97	80
25	88	3.60	1.22	
30	88	4.36	1.01	89
June 26	95	4.93	0.96	85
Nov. 23	88	4.65	0.94	97

Splenectomy, April 21, 1934.

CHART 2.—CURVES OF OSMOTIC RESISTANCE OF ERYTHROCYTES. CASE 1.



that the osmotic resistance was exceptionally low, hemolysis beginning in the solutions very close to the strength of physiologic salt solution. The curve of the erythrocyte diameters was monoapical with the peak at 6.30 μ. It was asymmetrical with a negative index of asymmetry (I), the extent of the variation (D) was greatly increased, the mean diameter (σ) much diminished and the standard deviation (σ) scarcely increased. The curve of reticulocyte diameters was biapical, with a microcytic peak at 6.82 μ and a normocytic peak at 7.87 μ. The curve of osmotic resistance was monoapical, with the peak at the point of 1.9% of sodium sulphate, producing 40% hemolysis. Beside this peak at 1.9% sodium sulphate, there were found two large groups of cells with resistance either greater or less than 1.9%, so that the extent of variation of the curve was greatly increased. In general the resistance of the erythrocytes was less than that of the normal minimum (1.4%).

Splenectomy produced not only a rapid disappearance of the icterus but a progressive decrease of anemia. Examination of the erythrocytes after the operation showed a rapid decrease of the spheroidal forms and of the spheroidal reticulocytes particularly. Also there appeared a peak of normocytic elements in the curve of erythrocytic diameters in addition to the preëxisting peak of microcytic elements. Thus the curve of erythrocyte diameters became biapical, while the reticulocyte curve remained monoapical, preserving its normocytic peak. The curve of osmotic resistance quickly lost the group of cells with the lowest resistance and became biapical by the formation, on the slant of a peak rather close to that which was already present, of a second peak of more resistant cells, even though still of a resistance below that of a normal minimum.

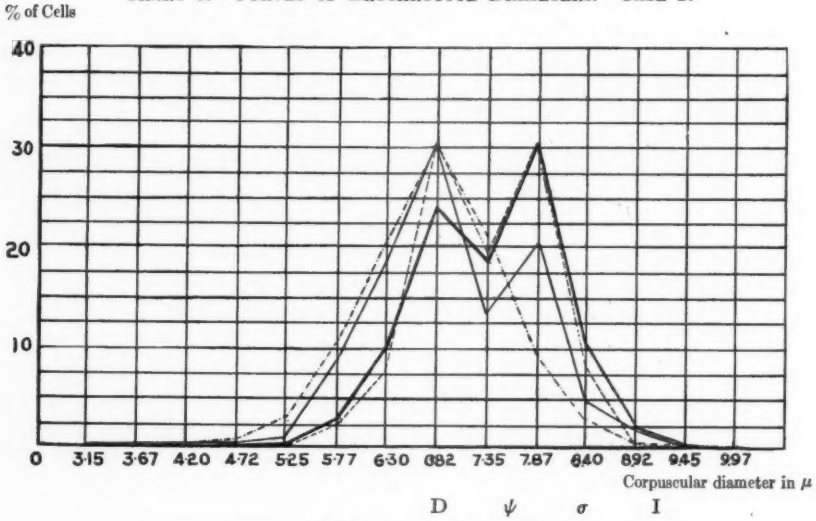
The normocytic peak of the curve of red cell diameters increased steadily at the expense of the microcytic curve until the curve became monoapical with a normocytic peak. It should be noted, also, that in the curve of osmotic resistance the biapical feature persisted more than in the curve of erythrocytic diameters. Also, while the left-hand peak of the curve maintained a fairly fixed situation, the right-hand peak gradually moved further to the right; in other words, approached a normal position. This had not been actually completed at the time of the last examination; however, there was obtained a hemolysis curve that was fairly near normal, whether this was obtained by the transformation of a biapical to a monoapical by complete disappearance of the left-hand peak, or as judged by the situation of the peak of hemolysis.

In any case, the approach toward normal of the diameters of the newly formed corpuscles appeared very soon after splenectomy. The approach toward normal of the osmotic resistance, on the other hand, seemed to make its appearance more slowly and was not complete even 7 months after the operation. Thus at the end of this period we were not able to speak of normal erythropoiesis in

all its aspects, but only from the point of view of the erythrocytic diameters.

In the second case the postoperative behavior was somewhat different from that of the first. In short, though there was a rapid disappearance of the icterus with increase in strength and coincident feeling of well-being and a decrease of the anemia (resulting finally in a hyperglobulia, even though of slight degree), the return of the curves of diameters and osmotic resistance to normal was not observed.

CHART 3.—CURVES OF ERYTHROCYTE DIAMETERS. CASE 2.



		D	ψ	σ	I
—·—·—·—	2. V.34	5,77	6,80	0,79	−0,2
———	13.VI.34	5,77	7,01	0,82	+0,2
▬▬▬	25.VI.34	5,25	7,36	0,74	+0,06
— — — — —	12.XII.34	6,82	7,29	0,72	+0,2

Dates.	Hb.	R.B.C., mill. per c.mm.	Color index.	Corpuscular volume, cubic micra.
May 2	52	3.20	0.81	86
June 13	70	3.58	0.98	
25	78	4.40	0.88	
Dec. 12	95	5.56	0.85	

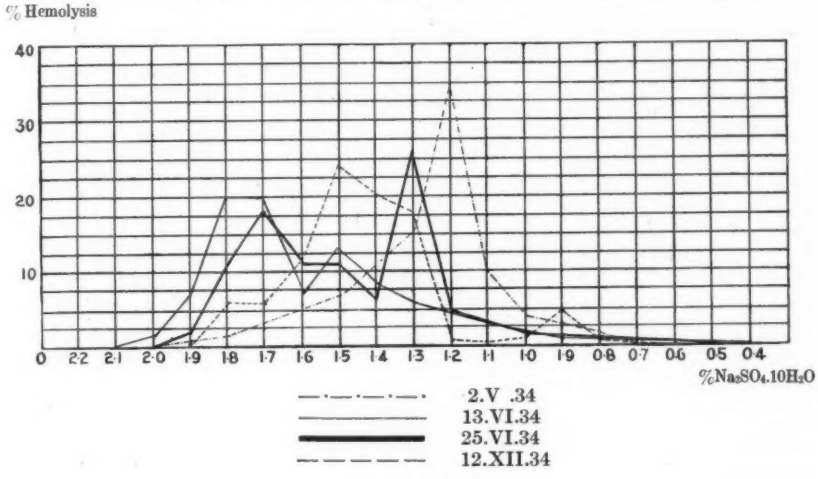
Splenectomy, June 6, 1934.

The curve of red cell diameters (Chart 3) in the period before the splenectomy was monoapical, with a microcytic apex, and exhibited an increased extent of variation. A notable decreased mean diameter, an increased standard deviation (σ) and a negative index of asymmetry. The hyperchromic microcytes made up more than one-half of the globular mass.

The curve of osmotic resistance (Chart 4) was monoapical, with the peak (amounting to about 35% hemolysis with 1.2% of sodium

sulphate) in a position that was almost normal. The minimal resistance, however, was notably diminished and the extent of variations of the curve was, therefore, not greatly increased. The corpuscular population, considered from the point of view of osmotic resistance, thus appeared in a large proportion to be fairly near normal.

CHART 4.—CURVES OF OSMOTIC RESISTANCE OF ERYTHROCYTES. CASE 2.



After splenectomy there appeared in the curve of red cell diameters a small normocytic apex beside the microcytic apex; but in the curve of hemolysis the extent of variations was increased through the appearance of a new class of cells with a lower resistance, and all the percentages of hemolysis in the left-hand part of the curve were thereby notably increased. Thus it followed that, while the curve of red cell diameters showed improvement as represented by the the heightening of the normocytic peak, which became higher than the microcytic peak, and by the marked diminution in the number of the spheroidal microcytes, while the percentage of reticulocytes and the figures for the curve of reticulocyte diameters returned to normal limit, the curve of osmotic resistance continued to exhibit an abnormal behavior, in that it appeared biapical (the 2 apices appeared, respectively, at the concentration of 1.7% and 1.3% of sodium sulphate).

This abnormal behavior of the resistance of the erythrocytes corresponds closely to the behavior of a case in which at the last blood examination, made about 6 months after splenectomy, the curve of red cell diameters continued to be biapical but with a worse picture than in the preceding examination. This was due to the fact that the microcytic peak had now become of the same height

as the normocytic peak, with an increase in percentages of the spheroidal microcytes. Also in the curve of hemolysis the abnormal position of the principal peak persisted, being localized in the concentration of 1.5% of sodium sulphate; in other words, in proximity to the minimal resistance of a curve of normal hemolysis. The change for the worse of some of the hematologic data in this case can probably be related to the reactivation of a hyperhemolysis in the organs of the retieulo-endothelial system accessory to the spleen.

Thus the picture presented after splenectomy is characterized by biapicality of the curves of red cell diameters and of their osmotic resistance. In the case that was apparently cured there was observed the rapid appearance of a normocytic population in addition to the microcytic cells of lowered resistance. The normocytic population made its immediate appearance with normal diameters; while the curve of the values for osmotic resistance immediately became biapical, a change which denoted the division of the population into two distinct groups of different characters. In this curve the return of a peak in normal or almost normal position was delayed for several months after operation. We then found that both the curve of red cell diameters and the curve of osmotic resistance became monoapical again through the superposition of a normal population on the remnants of the preëxisting pathologic population. More interesting was the fact that the presence of the two peaks in the curves of red cell diameters and resistance was also found in the case which acquired a clinical but not a biologic cure. In this case the biapicality of the curve of red cell diameters never disappeared to give way to a monoapical condition with the peak in normal position. The biapicality of the curve of resistance had a distinctly different form from that of the case that went on to cure.

Conclusion.—The interest in these observations consists in the demonstration of the existence of an approximate cure hematologically, as represented by the appearance of a persistent normocytic reaction of the marrow, even in those cases of hemolytic icterus which do not seem to have been completely cured after splenectomy, as evidenced by the persistence of microcytosis and of erythrocytic fragility, even though slight. We emphasize that the very rapid stabilization of the biapicality of the curves of red cell diameters and osmotic resistance after splenectomy documents in the clearest manner the capacity of the bone marrow to produce normal cells, at least from the point of view of their diameters. This observation is not favorable to the hypothesis that the spheroidal microcytosis represents a constitutional defect of erythropoiesis. In our opinion, it is evidence in favor of the view that, with the cessation of hyperhemolysis, that state of affairs disappears which transforms into an actuality the potential disposition of the bone marrow to form pathologic erythrocytes.

BIBLIOGRAPHY.

Banti, G.: La splenomegalia emolitica, Sperimentale, **66**, 91, 1912.

Banti, G.: La splenomegalia emolitica anemopoietica, Ibid., **67**, 323, 1913.

Bell, J. R., Thomas, F. K., and Means, J. H.: Studies on Red Cell Diameter in Health and Pernicious Anemia, J. Clin. Invest., **3**, 229, 1926.

v. Boros, J.: Über Grösse, Volumen und Form der menschlichen Erythrocyten und deren Zusammenhang. II Mitt. Über die Mikrocytose beim hämolytischen Icterus. Maygar Orvosi Arch., **26**, 171, 1925. (Autoreferatin: Kongresszentralblatt, f. ges. inn. Med., **40**, 69, 1925.)

Brugsch, J. T.: Beiträge zur Pathologie der Erythrocytengrössen, Folia hæmatol., **51**, 261, 1934.

Ceconi, A.: Vecchio e nuovo in tema di ittero emolitico, Ann. Clin. Med., **10**, 253, 1920.

Cheney, W. F., and Cheney, G.: Chronic Hereditary Hemolytic Jaundice: With a Report of 8 Cases and Notes on Measurement of the Size of Erythrocytes, Am. J. Med. Sci., **187**, 191, 1934.

Gamna, C.: L'anisocitosi dei globuli rossi del sangue nel suo significato patologico e diagnostico, Minerva med., **6**, 725, 1926.

Günther, H.: Die klinische Bedeutung der Grössenbestimmung der Erythrozytendurchmesser, Deutsch. Arch. f. klin. Med., **161**, 18, 1928.

Haden, R. L.: The Mechanism of the Increased Fragility of the Erythrocytes in Congenital Hemolytic Jaundice, Am. J. Med. Sci., **188**, 441, 1934.

Meulengracht, E.: Der chronische hereditäre hämolytische Ikterus, Leipzig, Thieme, 1922

Micheli, F.: Unmittelbare Effekte der Splenektomie bei einem Fall von erworbenem hämolytischen splenomegalischen Ikterus Typus-Hayem-Widal (Splenohämolytischer Ikterus), Wien. klin. Wchnschr., **24**, 1269, 1911.

Micheli, F.: Effetti immediati della splenectomia in un caso di ittero emolitico splenomegalico acquisito tipo Hayem-Widal, Clin. med. ital., **1**, 453, 1911.

Micheli, F.: Relazione al XXXV Congr. Soc. Ital. Med. Int., Genova, 1929; Le splenomegalie emolitiche, Il Policlinico. sez. pratica, **36**, 1683, 1929.

Momigliano-Levi, G., and Bairati, A.: Conseguenze immediate e remote della splenectomia sulle curve eritrocitometrica, reticolocitometrica e di resistenza osmotica dei globuli rossi in casi di ittero emolitico constituzionale, Arch. Sci. Med., **59**, 717, 1935.

Naegeli, O.: Blutkrankheiten und Blutdiagnostik, Berlin, Julius Springer, 1931.

Pearce, R., Austin, J. H., and Krumbhaar, E. B.: The Relation of the Spleen to Blood Destruction and Regeneration and to Hemolytic Jaundice, J. Exp. Med., **16**, 363, 1912.

Ponder, E., and Millar, W. G.: The Measurement of the Diameters of Erythrocytes, Quart. J. Exp. Physiol., **14**, 67, 1924.

Price-Jones, C.: The Diurnal Variation in the Size of Red Blood Cells, J. Path. and Bact., **23**, 371, 1919–1920.

Toyoda, T.: Zellstudien bei angeborenem hämolytischem Ikterus, Folia hæmatol., **29**, 65, 1923.

BIOPSY OF THE STERNAL BONE MARROW.

Its Value in the Study of Diseases of Blood-forming Organs.

By William Dameshek, M.D.,

Associate Physician, Beth Israel Hospital,
Boston, Mass.

(From the Department of Pathology and the Medical Clinic, Beth Israel Hospital.)

With constantly increasing knowledge in the field of hematology, it becomes more and more evident that the blood picture is not always an accurate reflection of the underlying abnormalities in the

blood-forming organs. The cells in the circulating blood are derived from the bone marrow, the lymphoid tissues and the reticulo-endothelial system. The number of the cells and their differential relationship to each other depend not only upon the phenomena of growth and destruction, but upon important factors governing their release from the hematopoietic centers. Particularly is this true in the case of the bone marrow. The peripheral blood may show all the features suggesting a hypoplastic condition of the bone marrow (anemia, leukopenia, thrombocytopenia), and yet the marrow itself may be intensely hyperplastic. This is the case in both pernicious anemia and primary hypochromic anemia.[1] The condition of the marrow may be identical in 2 cases of myelosis, although the peripheral leukocyte count in 1 may be 200,000, in the other 2000 per c.mm. The most marked leukopenic conditions may be associated with a "pyoid" marrow ("maturation arrest"[2]).

It has, furthermore, become evident that the same blood picture may be brought about by a number of diverse pathologic conditions. Thus: anemia, leukopenia and thrombocytopenia may be associated not only with aplastic and hypoplastic anemia, but with pernicious anemia, primary hypochromic anemia, the various aleukemic leukoses, Hodgkin's disease, lymphosarcoma invading the marrow, metastatic carcinoma, Gaucher's disease and possibly Banti's disease. It is true that certain clues in either the clinical laboratory or hematologic findings usually permit an accurate diagnosis, but an occasional case presents itself in which all efforts at exact diagnosis are at an *impasse*. It is here that the value of the bone-marrow biopsy as a diagnostic procedure has become increasingly important.

Besides its obvious importance in clinical diagnosis, biopsy has been found of great value in the study of the various "blood" diseases. By focussing attention on this all too poorly studied tissue, it has made the pathologist conscious of the unusually interesting histologic pictures which may be present, most reliance in the past having been placed on the gross appearance of the marrow. Special studies of the bone marrow in various diseases are being made and rapidly adding to the extent of our knowledge of the once mysterious "blood diseases."

Methods and Material. The first clinical marrow biopsies were performed, in 1908, by Ghedini.[3] Wolff,[4] in 1903, had already utilized the biopsy in experimental animals and pointed out that the method might be of clinical value. Ghedini,[3] Spuler and Schittenhelm,[5] in 1913, Zadek,[6] in 1921, Morris and Falconer,[7] in 1922, all used the tibial marrow, which is not only difficult of approach but often gives negative results. Impetus was given these studies by Seyfarth,[8] in 1923, when he introduced puncture of the sternum. This bone is easily accessible, its anterior lamella is only 5 mm. in thickness, and it can readily be punctured by a small hand trephine. Weiner and Kaznelson,[9] in 1926, extended Seyfarth's few observations, and in the same year Escudero and Varela[10] gave their first reports indicating

the diagnostic value of the sternal bone-marrow biopsy. The results of their 9 papers are reviewed in their report of 1932.[23] Peabody,[11] in 1926, was still utilizing the tibia in his studies of the bone marrow in pernicious anemia, but since then all the reported studies have been made on the sternum. Arinkin,[12] in 1929, modifying Seyfarth's method by introducing a hollow needle into the sternal marrow cavity and removing some of the liquid or semiliquid marrow, was able to study 180 cases. Arjeff,[13] in 1931, modified Arinkin's method slightly, and Tuschinsky and Kotlarenko,[14] in 1932, and Tempka and Braun,[15] in the same year, carried on investigations (using Arinkin's technique) of typhoid fever and pernicious anemia. Isaacs,[16] in 1930, studied the "physiologic histology" of the sternal bone marrow and Pokrowsky[17] correlated the state of the reticulocytes in the marrow, with those in the peripheral blood. Recent reports have been made by Barta[18] (22 cases), Nordensen[19] (170 cases with Arinkin's technique), Kossirsky,[20] Spartaco,[21] and Custer.[22]

Most of the investigations have been carried out with the semiliquid material obtained either with a hollow needle or by curette following the use of Seyfarth's trephine. Smears of this material have been studied as with the blood. Custer,[22,24] who has reported systematic observations of the bone marrow both from postmortem and biopsy studies, emphasizes the value of the study of properly fixed sections. In the present investigation,

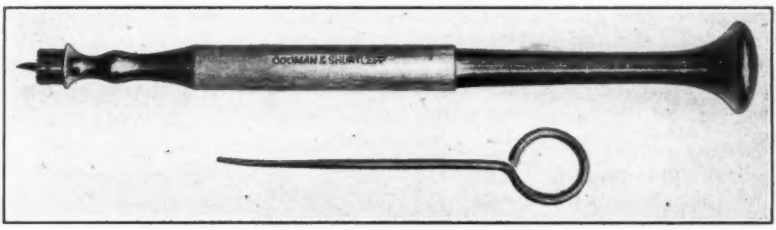


FIG. 1.—The bone marrow trephine (slightly less than actual size), and stilet for extraction of the plug of bone from the "crown."

Seyfarth's technique has been utilized, both smears and sections being prepared. About 125 biopsies have been performed in miscellaneous hematologic conditions. Seyfarth's trephine, slightly modified, was made for us by Codman and Shurtleff, of Boston (Fig. 1). It is essentially a small, steel hand trephine such as is used in trephining the cranium of cats and dogs, the essential feature being a saw-toothed crown, 5 mm. in diameter and 5 mm. long to the bevelled edge. A central protruding cutting edge is present, and small holes at the base of the crown allow entrance of a stilet for the purpose of extracting the bone which is contained after biopsy. I have added a handle at the top of the instrument, to allow a better grasp and more sustained pressure. The sternum is used on account of its accessibility and thin anterior lamella. The procedure is done under aseptic precautions, rubber gloves and sterile gowns being worn. Novocain, 1%, is used as a local anesthetic, the skin over the midsternum in the region of the third or fourth intercostal spaces being infiltrated. A 2- to 4-cm. incision is made directly in the midline, the edges of the wound being retracted with Allis forceps. The periosteum, after being infiltrated with novocain, is incised and retracted by the use of a small periosteal elevator. The bone-marrow trephine is now placed directly over the bare surface of the bone, slight pressure is made, and with a rotating motion from side to side, the marrow cavity is entered. At the moment of entrance, a

"give" is felt, as when entering the spinal canal. With a slight rocking motion, the trephine is removed together with its enclosed plug of bone. The resultant cavity is carefully scooped out by means of a fine curette, such as is used in ophthalmologic surgery, and the soft marrow thus obtained is spread out as with blood smears on sterile glass slides. Touch or imprint preparations are also made either from the plug of bone in the trephine or from small bits of bone removed by curette. These are very gently smeared on glass slides. The wound is closed with one deep silkworm-gut suture and 2 to 4 horse-hair skin sutures.

Two types of bone-marrow preparations are obtained by this method: sections and smears. The small plug of sternal bone (5 mm. in diameter by 5 mm. in length) is immediately placed into 100 cc. of Zenker's fixative solution containing 5 cc. of glacial acetic acid. After 48 hours, there is usually sufficient decalcification so that microscopic sections can be cut. In rare instances, nitric acid must be used for decalcification. The sections are then run through as in routine pathologic work, and stained with eosin methylene blue. Hematoxylin and eosin may be used, but this staining combination does not give as clear cellular detail. The sections are invaluable for a general picture of the bone-marrow relations, and for the proper understanding of normal or abnormal islands of hematopoietic cells. However, for exact cytologic study the marrow smears cannot be excelled. Wright's stain, diluted half and half with absolute methyl alcohol is used, the stain being allowed to remain for 2 minutes before water is added, the mixture of stain and water remaining for 4 to 8 minutes. Giemsa's stain followed by clearing in xylol, has lately been found much more satisfactory. Differential counts of the marrow smears and sections are made, the smears usually being far more satisfactory for this procedure. The following cell types are set down:

Nucleated red blood cells:
- Normoblasts.
- Erythroblasts.
- Pro-erythroblasts.
- Megaloblasts
- Promegaloblasts } in pernicious anemia.
- Erythrogones

White blood cells:
- Mature neutrophils.
- Metamyelocytes.
- Myelocytes.
- Pre-myelocytes.
- Myeloblasts.
- Eosinophils.
- Histiocytes.

Megakaryocytes.

Differentiation of the various cell types is not a simple matter and can only be mastered by long practice. It is probably best to begin by the careful cytologic study of the peripheral blood from cases of chronic myelosis (myelogenous leukemia).

The white blood cells are tabulated under the respective headings as noted above. These are counted in successive oil-immersion fields, each type of cell being searched for, and its number being recorded. The nucleated red blood cells in the same fields are also recorded. The ratio of nucleated red blood cells to white blood cells is obtained after a suitable number (200 to 500) of white blood cells are counted, and the differential percentages of each type of white blood cell are calculated.

The Normal Marrow. The most careful studies of the normal marrow have been made by Custer,[22,24] who compared the marrow from the various bones at different ages. He found that the

marrow from different bones varied in cellularity; that the sternum under normal conditions always contained cellular marrow and was most suitable for biopsy study, but that marrow from the vertebræ was the most highly cellular, the more constant in cellular composition and more suitable for postmortem study. In the present study, no biopsy specimens were obtained from entirely normal subjects,* so that standards for normality were necessarily derived from the study of postmortem material. The bone marrow was routinely examined from a large number of autopsies. Usually marrow was obtained from one of the ribs by expressing some of the soft material from a cut end. This made decalcification in nitric acid unnecessary. Fixation was made in Zenker's solution, paraffin sections being run through in the ordinary way and stained with eosin methylene blue. The best specimens were those obtained within a few hours after death. Specimens obtained 12 hours or more after death were often difficult to study for cellular detail. Unless autopsy was performed within an hour or two after death, the sections were usually decidedly inferior to those obtained at biopsy. Bone-marrow smears from autopsy specimens were ordinarily of little value.

It is almost impossible to obtain a normal marrow from an autopsy specimen, since death, unless accidental, is due to some definite cause and is frequently associated with a terminal infection. However, since the gross abnormalities, due to such "blood" diseases as leukemia and pernicious anemia, are usually absent, it is possible to obtain from the study of a large number of specimens a fairly accurate idea as to the relative percentages of various cells and the ratio of the nucleated red blood cells to white blood cells.

Results. From a study of about 200 bone-marrow sections obtained at autopsy, it is possible to present the following figures as representing the approximate cellular constituents found in the normal (rib) marrow:

Ratio of nucleated red blood cells to white blood cells: approximately 1 to 1 (variation from 0.6 to 1 to 1.2 to 1).

Differential Count of the White Blood Cells:

Mature neutrophils, 2 to 5%.	Pre-myelocytes and myeloblasts, 1 to 5%.
Metamyelocytes, 20 to 40%.	Eosinophils, 1 to 5%.
Myelocytes, 30 to 50%.	Histiocytes, 1 to 2%.

Differential Count of the Red Blood Cells:

Normoblasts, 80%.	Erythroblasts, 20%.

The megakaryocytes are sprinkled throughout the section, 2 to 10 usually being seen in counting 300 white blood cells (0.7 to 3.3%).

* Bone marrow which appeared to be entirely normal was obtained from a few patients with malignant hypertension.

A. Complications. Biopsies were done in a variety of hematologic conditions, ranging from severe anemia to polycythemia and from agranulocytosis to leukemia, as well as in cases presenting marked reduction in blood platelets. Two slight complications were encountered. In a case of diffuse acute lupus erythematosus, the skin wound failed to heal properly; in a case of chronic myelosis, a moderate degree of hemorrhage took place when the skin sutures were removed. Oozing at the time of operation in cases associated with marked reduction in blood platelets was always controlled by pressure. In no case was it necessary to use bone wax, although its use was considered in one or two instances.

B. Classification of Cases and Description of Bone-marrow Findings. The following is a classification of the diseases in which biopsy was done:

Pernicious anemia.
"Primary" hypochromic anemia.
Secondary hypochromic anemia.
Congenital hemolytic anemia.
Aplastic anemia.
Hypoplastic anemia.
Myelosis (myelogenous leukemia).
  Chronic leukemic.
  Chronic aleukemic.
  Acute leukemic.
  Acute aleukemic.
Lymphadenosis (lymphatic leukemia).
  Chronic leukemic.
  Chronic aleukemic.
  ? Chronic leukemic.
Reticulosis (monocytic leukemia).
Acute leukemic.
Chronic aleukemic.
Agranulocytosis.
Polycythemia vera.
Purpura hæmorrhagica.
Hodgkin's disease.
Lymphosarcoma metastasized to marrow.
Banti's disease.
Lupus erythematosus acuta.
Enterogenous cyanosis.
Chronic nephritis.
Malignant hypertension.
Hemochromatosis.

Since this paper deals chiefly with the diagnostic value of the bone-marrow biopsy, no detailed descriptions of the findings at biopsy in the various conditions classified above will be given. However, a few general remarks (limited to what was actually found at biopsy) will be made about each condition in which a biopsy was done.

Pernicious Anemia. Fourteen biopsies were performed. In 5 cases, biopsies both before and after treatment were made. In relapse, the marrow is characteristic: hyperplastic, without fat cells, and presenting large numbers of large embryonic nucleated red blood cells (promegaloblasts and megaloblasts). These are often present in "islands" and mitotic figures are numerous. Numerous cells resembling small lymphocytes, which have been called "erythrogones" are seen. Histiocytes are increased in number and apparent transitions between these embryonic cells and the promegaloblasts can be seen (Fig. 2). The percentage of normal nucleated red blood cells is

FIG. 2.—Photograph of water-color paintings of red blood cells observed at sternal bone-marrow biopsy in a case of pernicious anemia in relapse. The cells, numbered 1 to 15, inclusive, illustrate what appear to be transitions in the development of the red blood cell of pernicious anemia from the histiocyte to the mature macrocyte. 1, Typical histiocyte (hemohistioblast); 2, 3*a* and 3*b*, early promegaloblasts (these cells retain many of the features of leukocytes); 4, 5 and 6, promegaloblasts; 7 and 8, megaloblasts; 9 and 10, proerythroblasts; 11, 12 and 13, erythroblasts; 14, normoblast; 15, erythrocyte (macrocyte); 16, "erythrogones" (lymphoid-looking cells found in pernicious anemia); 17*a*, 17*b*, 17*c*, 17*d*, megaloblastic cells in various types of mitosis.

UNIV. OF MICH.

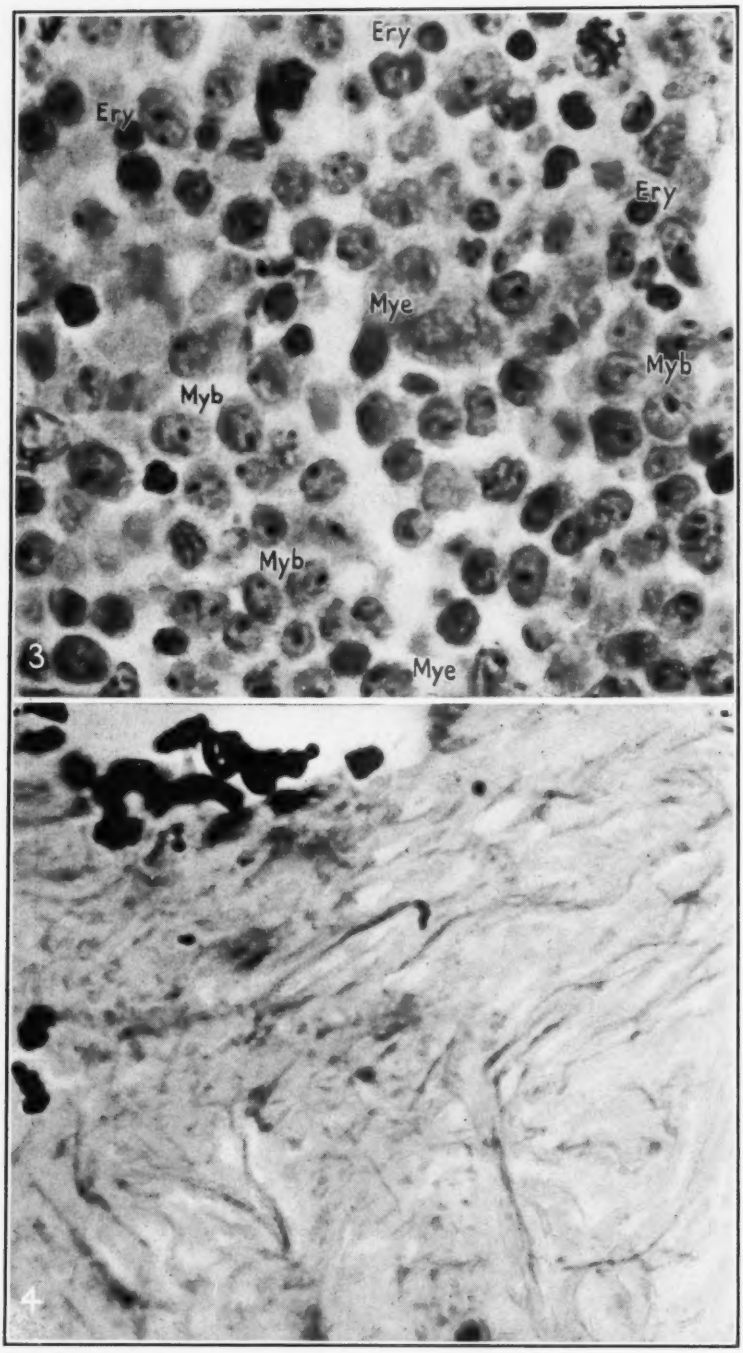


FIG. 3.—Photomicrograph of section of sternal bone marrow removed at biopsy in Case M. C. (Table 1). Aleukemic myelosis. (× 985.) Note the large number of proliferating myeloblasts with prominent nucleoli (*Myb*), the few myelocytes (*Mye*), and the marked reduction in nucleated red blood cells (*Ery*).

FIG. 4.—Photomicrograph of section of sternal bone marrow in Case M. G. (Table 3). Lymphosarcoma of spleen metastasizing to bone marrow. Smears show no marrow cells. Sections show replacement of normal marrow tissue by loose fibrous tissue. (× 985.)

UNIV. OF MICH.

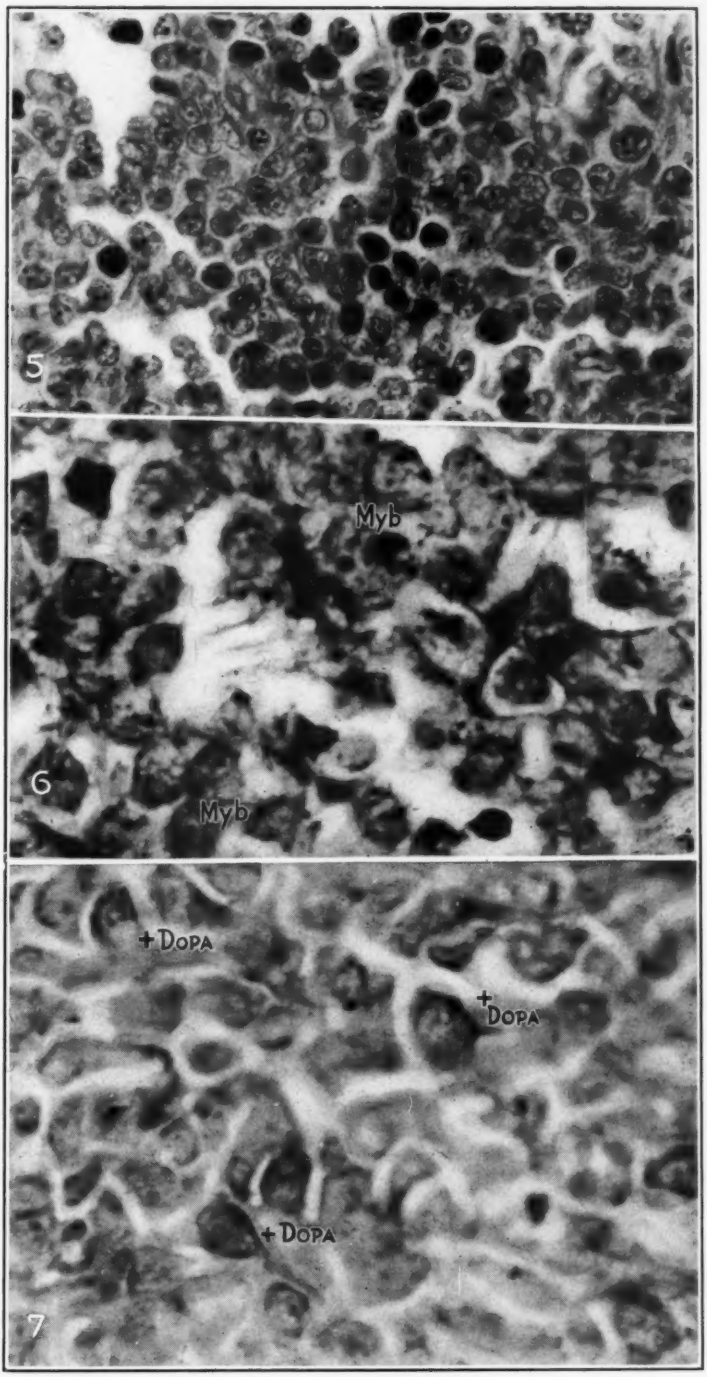


FIG. 5.—Photomicrograph of section of spleen removed at operation in Case M. G. (Table 3). Complete replacement of splenic architecture by rapidly proliferating primitive cells; lymphoblasts. (× 700.)

FIG. 6.—Photomicrograph of section of sternal bone marrow in Case F. L. (Table 4). Myelosarcoma (chloroma) with terminal aleukemic myelosis. (× 985.) Stuffing of marrow cavity with proliferating myeloblasts (*Myb*). Rare erythroblastic cell or megakaryocyte.

FIG. 7.—Photomicrograph of section of tumor of uterus removed at operation in Case F. L. (Table 4). Myelosarcoma of uterus. (× 985.) Dopa stain. Note the neoplastic process composed of embryonic cells (myeloblasts), many of them showing a positive "dopa" reaction.

UNIV. OF MICH.

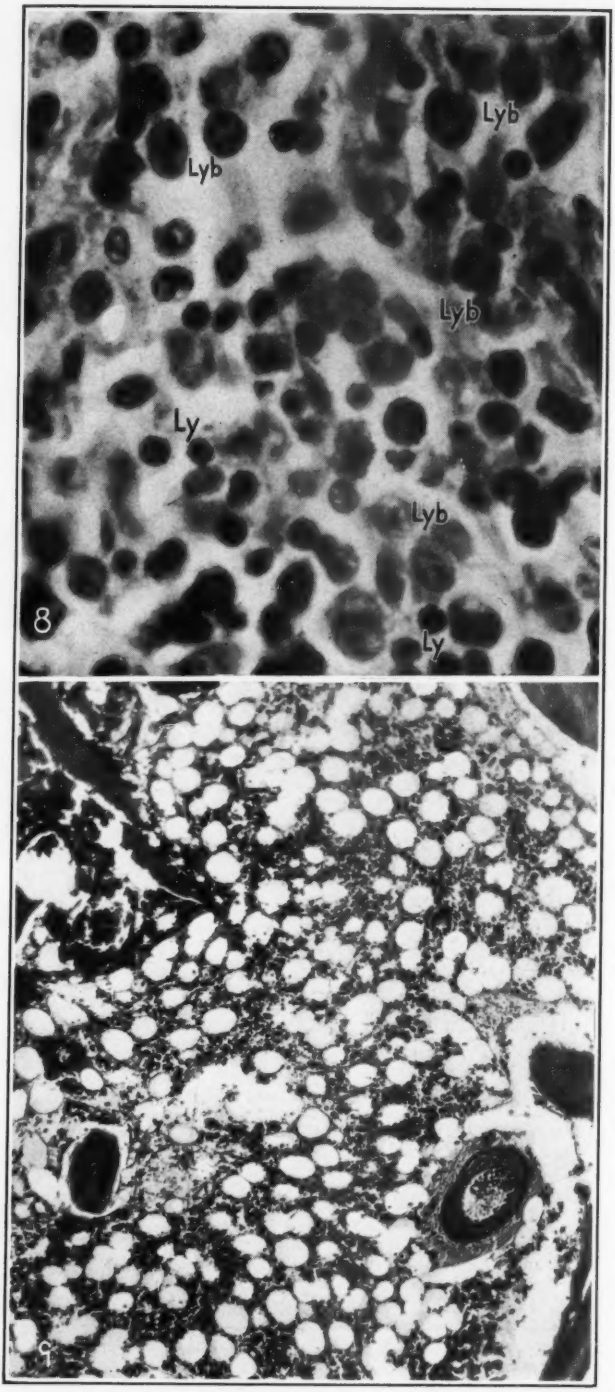


FIG. 8.—Photomicrograph of section of bone marrow in Case M. Z. (Table 5). Subacute aleukemic lymphadenosis. (× 985.) Note the large number of lymphoblasts (*Lyb*) and lymphocytes (*Ly*) infiltrating the marrow tissue.

FIG. 9.—Photomicrograph of section of bone marrow in Case Ellen O'C. (Table 6). Hypoplastic anemia; arteriosclerosis. (× 70.) Note the marked increase in number of fat cells (sternal marrow). At the right is seen an arteriole showing evidences of sclerosis.

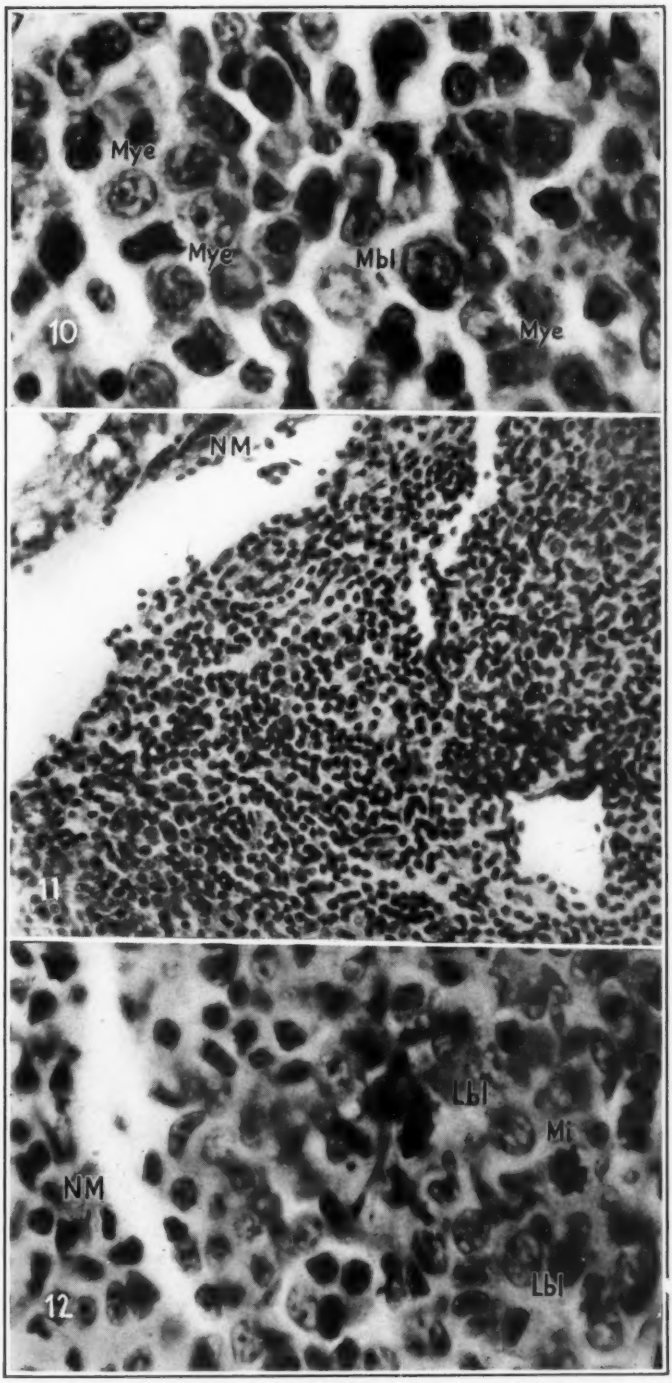


FIG. 10.—Photomicrograph of section of bone marrow in Case R. R. (Table 7) Aleukemic myelosis. (× 985.) Note the crowding of the marrow with granulocytic cells, myeloblasts (*Mbl*) and myelocytes (*Mye*), myelocytes predominating.

FIGS. 11 and 12.—Photomicrographs of section of bone marrow in Case E. S. (Table 8). Lymphosarcoma metastasizing to bone marrow. Fig. 11, low power (× 300) and Fig. 12, high power (× 1000). Note the mass of proliferating cells infiltrating and invading the normal marrow tissue (*NM*). The proliferating cells are identified as lymphoblasts (*Lbl*). A mitotic figure (*Mi*) is seen.

markedly diminished, their number varying with the degree of relapse. In severe relapse, only a few erythroblasts and normoblasts are seen. After the institution of liver treatment, the marrow resumes to great extent its normal appearance; normoblasts are now the predominating cell and only a rare megaloblast is seen. The white blood cells now become present in normal numbers, together with great diminution in the histiocytes and the "erythrogones."

Secondary Hypochromic Anemia. Of 3 cases studied, in 2 the anemia was associated with hypernephroma and the marrow showed hypoplasia of the erythroblastic tissue; in the other, with chronic hemorrhage the red cell-forming tissue was hyperplastic.

Primary Hypochromic Anemia. Kaznelson, Reimann and Weinner,[25] and I[1] have described the bone-marrow findings in this disease. The disease may be idiopathic in nature or may be associated with diverse etiological factors leading to a chronic iron deficiency state. Clinically there is anemia of low color index and of small red cells associated with achlorhydria. The bone marrow, despite the often striking anemia, is hyperplastic. There is great increase in the normal nucleated red cells (erythroblasts and normoblasts), megaloblasts not being found. I have likened the bone-marrow findings in this disease with those found in pernicious anemia.[1] The bone marrow in both conditions is, despite the anemia, hyperplastic, the red cells apparently being unable to mature properly unless the appropriate medication (liver extract in the one case, large doses of iron in the other) is given. Crowding of the marrow by increased formation of nucleated red blood cells results in some diminution in both the white blood cells and megakaryocytes.

Congenital Hemolytic Anemia. The bone marrow has been but little studied in this disease. Biopsies were done in 2 cases: in 1, the ratio of red blood cells to white blood cells was 0.4 to 1, and the percentage of erythroblasts was greatly increased (80%); in the other, the ratio of red blood cells to white blood cells was about 1 to 1, and here, too, there was a marked relative increase in erythroblasts (to 80%). In this case there was a definite increase in histiocytes, although no cells with phagocytosed inclusions could be seen.

Aplastic Anemia. Of 5 cases studied, in 4 severe cases the marrow was almost entirely converted to fat, only a few cells being present. In a fourth, due apparently to repeated "courses" or arsphenamin, there was almost complete absence of nucleated red blood cells (ratio of red to white blood cells, 0.075 to 1), although white blood cells were present in fairly large numbers. After several transfusions, this patient finally recovered completely.

Myelosis. In 10 cases studied, the findings varied directly with the type of the disease—whether acute or chronic. In the chronic type—leukemic or aleukemic—there was marked increase in leuko-

cytes, the ratio of red blood cells to white blood cells varying from 0.05 to 1 to 0.7 to 1. Differential count of the white cells was distinguished by a marked increase (often up to 40 to 50%) in myeloblasts, myelocytes, however, being present in almost normal numbers. The normal growth of red blood cells and usually of megakaryocytes is interfered with by the large numbers of proliferating white blood cells, although in one case large numbers of megakaryocytes were found. In the acute cases the marrow was overrun by large numbers of myeloblasts, frequently in mitosis, myelocytes and more mature neutrophils being but rarely seen. In this mass of cells there is almost complete disappearance of nucleated red cells and megakaryocytes. In 2 subacute cases the findings were intermediate between those of chronic and acute leukemia. Whether the white blood cell count was high or low (leukemic or aleukemic leukemia), the cellular picture in the bone marrow was found to be identical.

Lymphadenosis (*Lymphatic Leukemia*). The bone marrow in 6 cases of the chronic variety of this disease showed varying degrees of invasion with lymphocytes, with variable distortion of and interference with normal cell growth. In 1 case in which the diagnosis of early chronic lymphatic leukemia was suspected, because of long-standing absolute lymphocytosis (white blood cells, 15,000; lymphocytes, 70 to 80%), the marrow showed the presence of more lymphocytes than of ordinary bone-marrow white cells. There appeared, however, to be little interference with red blood cell growth.

Reticulosis (*Monocytic Leukemia*). I[26] have described the bone marrow findings in this third type of leukemia, which is distinguished hematologically by marked increase in monocytes and histiocytes. The acute type exhibits overwhelming proliferation of histiocytes, only a small amount of reticulum being present. In an example of the chronic aleukemic type which was studied, there was marked increase in reticulum with the presence of numerous giant cells.

Agranulocytosis. In 1 patient studied there was complete absence of mature neutrophils, metamyelocytes and myelocytes, the only remaining leukocytes being a few myeloblasts.

Polycythemia Vera. The bone marrow was studied in 4 patients with this condition, in whom the red blood cell count ranged between 7,000,000 and 9,000,000. In each case there was marked hyperplasia of both red and white blood cell forming elements, the ratio remaining normal (1 to 1). Fat cells were conspicuously diminished. Occasional islands of primitive nucleated red blood cells could be seen. The megakaryocytes were conspicuously increased in number. The bone marrow thus showed a generalized proliferation of its three elements: erythroblasts, meyloblasts and megakaryocytes.

Secondary Polycythemia. The polycythemia in this case (K.) was secondary to chronic cardiac and pulmonary disease. Approximately the same findings as were present in the "true" type of polycythemia were observed.

Purpura Hemorrhagica. In 1 chronic case in which the blood platelet count was 40,000 per c.mm., the bone marrow disclosed nothing remarkable. Megakaryocytes were present in normal number, although they appeared smaller than normal. This patient had a long remission after splenectomy, but is now again in relapse.

Hodgkin's Disease. Recent papers have directed attention to the generalized character of the lesions in Hodgkin's disease. In a recent paper I[26] have discussed the cell type involved and have presented reasons for assuming that it is of the reticulum cell (histiocyte) series. In 6 cases of Hodgkin's disease studied at biopsy, the leukopoietic elements in the bone marrow were markedly hyperplastic, the ratio of white to red blood cells being conspicuously increased. In each case there was marked increase in immature leukocytes. Thus, in case C. G., there were 12% myeloblasts and pre-myelocytes, in case A. M. these cells numbered 24.6% of the total leukocytes, and in case E. B., 36.2% of these cells were present. The histiocytes were increased only slightly in case C. G. and E. B. (2.8% and 2%, respectively), but were markedly increased in case A. M. to 24%. In the latter case the disease appeared to be more generalized than in the other two and was associated with marked anemia, leukopenia and splenomegaly. The megakaryocytes in this case were also greatly increased, as many as 7 being found in one oil-immersion field. These giant cells were normal in the remaining cases.

Lymphosarcoma With Metastasis to Bone Marrow. This is a rare lesion, although I have observed it in 5 cases. In 3 cases in which biopsy was done, the bone marrow showed almost complete absence of normal marrow tissue, with large numbers of lymphoblasts and a few lymphocytes.

Banti's Disease. The great majority of cases diagnosed as Banti's disease which I have seen have been found on more careful study to be some other disease, usually chronic aleukemic myelosis. In 1 case (S. W.) studied with bone-marrow biopsy, however, the diagnosis at present appears to be that of Banti's disease rather than that of aleukemic myelosis, as originally considered. In this case there was clinically several attacks of hematemesis, marked splenomegaly, leukopenia, thrombocytopenia and moderate anemia. Bone-marrow biopsy showed increase in white blood cell-forming elements, with increase in embryonic white blood cells (myeloblasts and pre-myelocytes) to 44%. The diagnosis in this patient is still in doubt, although Banti's disease appears to be at present the most probable.

Acute Lupus Erythematosus. The acute or disseminated form of lupus erythematosus appears to be a general disease rather than one limited to the skin. In 1 case in which biopsy was done there was, besides the skin lesions, splenomegaly, generalized lymph-node enlargement, leukopenia, thrombocytopenia and moderate anemia. The bone marrow disclosed a definitely hyperplastic marrow with small areas of necrosis affecting particularly the leukopoietic elements. There was an increase in reticulum cells throughout the section.

Enterogenous Cyanosis. In this highly unusual case there was clinically a slate-gray-blue color of the skin and mucous membranes, moderate hypochromic anemia and diarrhea, apparently due to pinpoint ulcerations in the rectum. There was a varying percentage of "inactive" hemoglobin, the oxygen-carrying hemoglobin (as determined by the Van Slyke-Neill oxygen capacity method) being much less than the total hemoglobin (as determined by the Wong iron method or the cyanhemoglobin method of Stadie). Spectrophotometric studies showed at times methemoglobin, at times sulphhemoglobin, at times both. The bone marrow showed hypoplasia of the red cell-forming elements, the ratio of nucleated red to white blood cells being 0.34 to 1. There was definite increase in histiocytes to 10%.

Chronic Nephritis. In 4 cases of chronic nephritis associated with more or less marked nitrogen retention and moderate to marked anemia, the biopsy in each case showed distinct hypoplasia of erythropoietic tissue, neither the leukopoietic elements nor megakaryocytes being affected.

C. The Use of the Bone-marrow Biopsy in Clinical Practice. At the beginning of this study, the bone-marrow biopsy was resorted to in almost every hematological case whether or not a diagnostic problem presented itself. In this way standards of comparison were obtained, together with actual information which had heretofore not been well documented. In the past 2 years, however, the biopsy has been chiefly utilized when diagnosis was actually in doubt and when it seemed probable that it could be settled by this test. Of the approximately 125 cases in which biopsy was done, the exact hematologic diagnosis remained in doubt in 26, even after careful clinical, laboratory and hematologic studies had been made. Of this group of 26, the diagnosis was definitely established at biopsy in 20; in 6, the diagnosis still remained in doubt even after biopsy. A short résumé of 18 cases in which diagnosis was difficult will be given, together with the findings at biopsy, only positive findings being reported. The following abbreviations will be used: R.B.C. (red blood cell count), W.B.C. (white blood cell count), N. (neutrophils), L. (lymphocytes), M. (monocytes).

Case Abstracts. 1. M. C. Seen with Dr. R. B. Buck at New England Baptist Hospital. *Pre-biopsy diagnosis:* unexplained anemia; ? agranulocytosis. *Biopsy diagnosis:* acute aleukemic myelosis (Table 1).

TABLE 1.—(CASE M. C.)

Clinical Findings.	*Blood Findings.*
History: female, aged 45. Weakness since July, 1928. September, 1928, pain in region of anus together with marked swelling. October 15, 1928, hemorrhoidectomy followed by increasing weakness and pallor.	Hemoglobin, 60 to 17%.
	R.B.C., 3.2 to 1.08.
	W.B.C., 4000 to 1700.
	Platelets, 100,000.
	Red blood cells: achromia +, anisocytosis ++, poikilocytosis ++.
Examination: necrotic ulceration of rectum, marked pallor.	Differential count: P., 4; L., 80%; M., 16%.

Final Clinical Diagnosis.

Agranulocytosis.
Unexplained anemia. (Previous diagnoses: typhoid fever, miliary tuberculosis, etc.)

Bone-marrow Biopsy.	*Further Findings.*
Many islands of actively proliferating myeloblasts. Conspicuous reduction in erythroblastic cells and in megakaryocytes. (Fig. 3.)	*Postmortem:* large spleen, with but little change microscopically. Bone marrow showed active hematopoiesis with many megakaryocytes.
Diagnosis: acute myelosis.	

Final Diagnosis.

Acute (aleukemic) myelosis.

2. RHODA L. B.I.H. 7287. *Pre-biopsy diagnosis:* chronic unexplained anemia; ? atypical lymphoblastoma; ? aleukemic lymphadenosis. *Biopsy diagnosis:* lymphosarcoma or lymphadenosis with bone-marrow invasion. *Final diagnosis:* chronic aleukemic lymphadenosis.

An American-Jewish girl, aged 4½ years, became nauseated 5 weeks before admission to the hospital, on August 19, 1930. She gradually became listless and pale. On examination she showed rather marked pallor, moderately enlarged cervical lymph nodes and a few small axillary lymph nodes. *Blood studies:* hemoglobin, 29%; R.B.C., 2,110,000; W.B.C., 2100; platelets, 274,000; reticulocytes, 0.4%. Differential count: N., 7%; L., 84%; M., 9%. Several lymphocytes were definitely abnormal and an occasional questionable lymphoblast was seen. *Bone-marrow biopsy* (September 17, 1930): almost complete replacement of the bone marrow by large numbers of lymphoblasts. In counting 1000 lymphoblasts only 3 myelocytes, 2 metamyelocytes, 1 mature neutrophil and 2 normoblasts were seen. *Course:* There was mild fever. The patient was given two transfusions of blood, ferric ammonium citrate and liver extract without appreciable effect. The liver gradually became enlarged. The patient was discharged in essentially the same condition as on entrance. In November, 1930, she began to improve, and there was rise in hemoglobin, erythrocyte and leukocyte counts to almost normal. There was continued improvement for about

6 months, but in March, 1931, she again became weak, listless and pale. At that time there was generalized enlargement of lymph nodes, liver and spleen; the leukocyte count was 12,000 to 15,000 per c.mm., with 80 to 90% lymphocytes. The patient died in April, 1931. Autopsy was not obtained. *Final diagnosis:* chronic lymphatic leukemia (aleukemic); ? lymphosarcoma with metastases to bone marrow.

3. Moses S. B.I.H. 5144. *Pre-biopsy diagnosis:* splenomegaly, ? type; Banti's disease. Secondary anemia. *First biopsy diagnosis* (January 25, 1930): hypoplastic marrow. *Second biopsy diagnosis* (April 28, 1931): chronic (aleukemic) meylosis.

A Jewish clothing peddler, aged 70, entered the hospital, on January 21, 1930, complaining of pallor, weakness and swelling of the abdomen of about 1 year's duration. Examination disclosed sallow-yellow pallor, ascites and a large thin spleen extending to the crest of the ilium; the liver was not felt. *Blood studies:* hemoglobin, 48%; R.B.C., 2,690,000; W.B.C., 3600; platelets, 140,000; reticulocytes, 3.5%. The red blood cells showed slight achromia, moderate anisocytosis and poikilocytosis. Differential count: N., 56% (8 band forms); L., 31%; M., 7%; E., 6%. *Interpretation of blood picture:* hypoplasia or destruction of bone marrow, ? type. *Bone-marrow biopsy* (January 25, 1930): ratio of nucleated R.B.C. to W.B.C., 1 to 0.64. Differential count of the W.B.C.: mature neutrophils, 7%; metamyelocytes, 26.8%; myelocytes, 30.7%; pre-myelocytes and myeloblasts, 22.2%; eosinophils, 15%. The bone-marrow sections showed nothing remarkable.

The patient was readmitted on April 16, having felt better until January, 1931. There were signs of cardiac decompensation with fluid at both bases, ascites and a large balottable spleen. The blood picture showed no material change from the previous year, *i. e.*, there was anemia, leukopenia and thrombocytopenia, interpreted as signifying a hypoplastic bone marrow, due to (1) ? "splenic anemia" with fibrosis, (2) myelogenous leukemia (aleukemic), (3) neoplastic metastasis to the marrow. A second *bone-marrow biopsy* was done on April 28. Parts of the section showed hyperplasia, the cell type being the myeloblast. Bone-marrow smears showed a ratio of W.B.C. to nucleated R.B.C. of 1.4 to 1, with 18% myeloblasts. *Course:* The cardiac decompensation improved. There was marked reduction in size of the spleen following Roentgen radiation. The patient is still being followed. The blood picture remains essentially the same.

4. Emma B. Seen with Dr. J. H. Pratt at New England Baptist Hospital. *Pre-biopsy diagnosis:* splenomegaly ? type; ? pernicious anemia. *Biopsy diagnosis:* chronic (aleukemic) myelosis.

A woman, aged 49, complained of increasing weakness, epigastric pain, and loss of weight, beginning in August, 1930. *Examination,* November 29, disclosed marked pallor, a red tongue denuded of coat, and a large spleen extending to the crest of the ilium. *Blood studies:* hemoglobin, 35 to 40%; R.B.C., 1,820,000 to 2,200,000; W.B.C., 1600 to 3400; platelets, 22,000 to 120,000; reticulocytes, 5.5%. Differential count of the W.B.C. showed: mature neutrophils, 46%; metamyelocytes, 18%; myelocytes, 0.8%; L., 22.8%; M., 11.6%. *Interpretation of blood studies:* a "destructive" condition of the bone marrow (anemia, leukopenia, thrombocytopenia), probably leukemic in type. *Bone-marrow biopsy* (November 29, 1930): a hyperplastic marrow with areas of proliferating myeloblasts. Differential count of the bone-marrow leukocytes: mature neutrophils, 2%; metamyelocytes, 19.5%; myelocytes, 19%; pre-myelocytes and myeloblasts, 51%; histiocytes, 4%. *Diagnosis:* chronic aleukemic myelosis. The

patient died on December 7, 1930, following severe hemorrhages from the lungs, throat and nose. Autopsy not obtained.

5. CHARLES M. Seen with Drs. Smart and Robinson, Laconia, N. H.* *Pre-biopsy diagnosis:* chronic unexplained anemia; relapsing fever. *Biopsy diagnosis:* ? generalized Hodgkin's disease. *Final diagnosis:* aleukemic reticulosis (Table 2).

TABLE 2.—(CASE C. M.)

Clinical Findings.	*Blood Findings.*
History: male, aged 39. Weakness, 5 months. Fever, relapsing in type, 3 months. Pallor, loss of weight, 2 months.	Hemoglobin, 55 to 30%. R.B.C., 2.83 to 1.80. W.B.C., 3500 to 1100. Platelets, 123,000. Reticulocytes, 1.4%.
Examination: pallor. Spleen just felt; One supraclavicular lymph node felt.	Red blood cells: achromia 0; anisocytosis ++; poikilocytosis ++; polychromatophilia +.
Laboratory findings: All negative.	P., 72.5% (8.5 "band forms"); L., 9.5%; M., 16% (histiocytes, 1); E., 1.5%.

Clinical Diagnosis.

"Destructive" process of bone marrow: ? lymphosarcoma; ? Hodgkin's disease. (Previous diagnoses: typhoid fever, malaria, agranulocytosis, etc.)

Bone-marrow Biopsy.	*Postmortem Examination.*
Dense tissue replacing almost entirely the normal elements; hyperplasia of reticulum cells; giant-cell formation. *Diagnosis:* ? Hodgkin's disease involving bone marrow.	Proliferation of reticulo-endothelial cells throughout entire body; liver, spleen, lymph nodes, bone marrow, omentum, etc.

Final Diagnosis.

Aleukemic reticulosis (generalized Hodgkin's disease?).

6. MITCHELL G. B.I.H. 3491. *Pre-biopsy diagnosis:* ? Banti's disease; chronic hypoplastic anemia ? type. *First biopsy diagnosis:* hypoplastic bone marrow. *Second biopsy diagnosis:* lymphosarcoma with invasion of bone marrow (Table 3).

7. MARTIN P. Boston Disp. 138552. *Pre-biopsy diagnosis:* pernicious anemia. *Biopsy diagnosis:* ? chronic lymphatic leukemia (aleukemic); ? lymphosarcoma with metastasis to bone marrow.

A man, aged 53, complained of vague pains in the joints, slight weight loss and spontaneously appearing ecchymoses, all of about 6 months' duration. *Examination* showed nothing but moderate pallor. There was no icterus; the tongue was normal; neither the spleen, lymph nodes nor liver were palpable. *Blood:* hemoglobin, 62%; R.B.C., 3,140,000; W.B.C., 4650; platelets, 161,000. Differential count of the white cells: neutrophils, 12%; lymphocytes, 88% (several very large lymphocytes; no lymphoblasts; monocytes, 0. The red cells showed no achromia and many macrocytes; average red blood cell diameter, 7.9 micra. *Other laboratory data:* gastric analysis showed 12 units of free hydrochloric acid after injection of histamin.

* This case has been fully described in a previous paper.[26]

Icterus index, 6. *Interpretation:* blood picture shows macrocytic anemia, probably pernicious anemia; very high percentage of lymphocytes unusual; presence of free hydrochloric acid in gastric juice makes diagnosis doubtful. *Bone-marrow biopsy: Smears:* ratio nucleated red blood cells to white blood cells, 0.02 to 1. Differential count of white blood cells: lymphocytes, 99.2%; granulocytes, 0.8%. *Sections:* fibrous marrow in parts; packing with lymphoblasts and lymphocytes in other portions; several mitoses. Rare normal marrow cell present. *Diagnosis:* ? lymphatic leukemia or lymphosarcoma metastasizing into marrow. Course: No improvement with parenteral liver therapy or large doses of iron. The patient escaped from observation.

TABLE 3.—(CASE M. G.)

Clinical Findings.	*Blood Findings.*
History: male, aged 13. November, 1928, recurring fever, weakness, swelling of joints. March, 1929, splenomegaly noted. *Examination:* Intermittent fever; pallor; moderate splenomegaly.	August, 1929: Hemoglobin, 58%. R.B.C., 3.31. W.B.C., 2000. Reticulocytes, 0.6%. Platelets, 60,000. Red blood cells: achromia +; anisocytosis ++; poikilocytosis ++. Differential: P., 61%; L., 37%; M., 2%.

Clinical Diagnosis.

Subacute bacterial endocarditis; Banti's disease; splenic anemia; ? Hodgkin's disease.

Bone-marrow Biopsy.	*Splenectomy.*
Bone-marrow biopsy 1: smears showed no marrow cells. Sections showed replacement of normal marrow tissue by loose fibrous tissue (Fig. 4, × 985). *Diagnosis:* fibrosis of marrow. *Bone-marrow biopsy 2* (after splenectomy): smears showed very few marrow cells. Almost all cells large, with very large nuclei. Oxidase stain negative. Apparent transitions to lymphocytes. Sections showed replacement of marrow by fibrous tissue in midst of which were present large primitive cells. *Diagnosis:* Fibrosis of marrow secondary to metastasizing lymphosarcoma.	*Spleen* (*Fig. 5*, × 700): complete replacement of splenic architecture by rapidly proliferating primitive cells; lymphoblasts. *Diagnosis:* primary lymphosarcoma of spleen. Autopsy not obtained.

Final Diagnosis.

Primary lymphosarcoma of spleen, metastasis to bone marrow, "myelophthisic" anemia.

8. SARAH F. Boston Disp. 276903. *Pre-biopsy diagnosis:* chronic aleukemic myelosis. *Biopsy diagnosis:* hypoplastic bone marrow. *Final diagnosis:* hypernephroma of left kidney with metastases.

A woman, aged 53, complained of weakness. *Examination* disclosed slight pallor, a large mass in the left upper quadrant of the abdomen diagnosed as spleen, and a liver edge palpable 3 fingers' breadth below the right costal margin. *Blood:* hemoglobin, 58%; R.B.C., 3,200,000; W.B.C., 5800. Red blood cells: slight achromia, slight anisocytosis and poikilocytosis. White blood cells: N., 82% (8 metamyelocytes); L., 12%; M., 6%. *Interpretation:* large spleen, slight anemia, probably chronic myelogenous leukemia (aleukemic). *Bone-marrow biopsy: Smears:* R.B.C. to W.B.C., 1.1 to 1. Leukocytes: mature N., 2.5%; metamyelocytes, 44%; myelocytes, 36%; myeloblasts, 9%; eosinophils, 3.5%. *Sections:* a hypoplastic marrow. *Later studies:* Intravenous urography showed large mass in abdomen to be kidney—confirmed by retrograde pyelography. Chest plates showed metastatic mediastinal shadows. Liver became larger and the patient died, January 30, 1932.

9. GEORGE A. B.I.H. 17396. *Pre-biopsy diagnosis:* ? aleukemic reticulosis (generalized Hodgkin's disease); ? aleukemic myelosis. *Biopsy diagnosis:* myelosis. *Final (postmortem) diagnosis:* generalized Hodgkin's disease (aleukemic reticulosis or aleukemic monocytic leukemia).

A man, aged 29, complained of anorexia, weakness and loss of weight of 10 months' duration and of bouts of fever and severe nightsweats of 3 months' standing. *Examination* revealed a temperature of 104° F., extreme pallor, generalized slight lymphadenopathy and a just palpable spleen. *Blood:* hemoglobin, 58%; R.B.C., 3,300,000; W.B.C., 4200; platelets, 170,000; N., 66% (24% metamyelocytes); L., 5%; M., 21% (13% histiocytes); unclassified cells, 7%. *Interpretation:* "destructive" process of bone marrow, possibly aleukemic reticulosis (13% histiocytes). *Bone marrow biopsy: Smears:* ratio of R.B.C. to W.B.C., 0.2 to 1. Differential count of the W.B.C.: mature N., 3.3%; metamyelocytes,4 1.1%; myelocytes, 32.1%; myeloblasts, 20.1%; eosinophils, 1.8%; histiocytes, 1.5%. *Sections* showed marked cellular proliferation, predominating cell being the myeloblast. *Course:* Temperature came to normal a few days after admission. The patient was given a course of Roentgen ray therapy over the legs and scapulæ and there was improvement for about 2 months. He returned to the ward in relapse, again with fever. The liver and spleen were larger, the red blood cells and white blood cells lower. Shortly thereafter, he was admitted to another hospital, where again the diagnosis of myelogenous leukemia was made after bone-marrow biopsy. Postmortem study, however, showed generalized Hodgkin's disease (aleukemic reticulosis).

10. FLORENCE L.* Seen with Dr. E. T. Fisher, Hahnemann Hospital, Worcester, Mass. *Pre-biopsy diagnosis:* ? agranulocytosis; ? acute aleukemic myelogenous leukemia; ? lymphosarcoma of uterus with metastasis to bone marrow. *Biopsy diagnosis:* acute myelosis. *Final diagnosis:* myelosarcoma (chloroma); terminal aleukemic myelosis (Table 4).

11. GLADYS M. Seen with Dr. C. Lawson at Rhode Island Hospital, Providence. *Pre-biopsy diagnosis:* ? agranulocytosis; ? aleukemic leukemia. *Biopsy diagnosis:* acute aleukemic myelosis.

A single girl, aged 21, became exhausted in May, 1932, and increasingly weak during July and August, 1932. A tooth was extracted on August 5. The face became markedly swollen, and there was almost constant bleeding from the tooth socket for 3 days. Weakness and pallor became rapidly worse, and on August 12 the patient was admitted to the hospital. *Examination* disclosed extreme pallor which was of a sallow-yellow tint. Several petechial spots were present on the buccal mucous membranes and the hard palate. The spleen was felt 2 fingers' breadth below the left costal margin, although the liver was not enlarged. The *blood:* hemoglobin,

* This case will be more fully reported at a later date.

26 to 33%; R.B.C., 1,300,000 to 1,800,000; W.B.C., 3400 to 2800. Differential count: granulocytes, 73% (mature neutrophils, 2%; metamyelocytes, 5%; myelocytes, 2%; pre-myelocytes, 8%; myeloblasts, 57%); lymphocytes, 23%; monocytes, 2%; histiocytes, 2%. The red blood cells showed slight achromia and moderate change in size and shape. The blood platelets were very much diminished, with several bizarre forms. *Interpretation:* bone-marrow destruction, probably myeloblastic in origin. The *bone-marrow biopsy* (August 15, 1932) disclosed a ratio of W.B.C. to R.B.C. of 1 to 0.7. Differential count of the W.B.C.: mature neutrophils, 1%; metamyelocytes, 8.5%; myelocytes, 12%; myeloblasts and pre-myelocytes, 77%; histiocytes, 1.5%. Oxidase stain of the myeloblasts positive. *Diagnosis:* acute aleukemic myelosis. *Course:* The patient rapidly grew worse and died on August 24, 1932.

TABLE 4.—(CASE F. L.)

Clinical Findings.	*Blood Findings.*
History: female, aged 33. *Hysterectomy* (for menorrhagia), May 2, 1932. Large tumor adherent to uterus and left ovary, encroaching on left ureter. Diagnosis: ? sarcoma. July 15, 1932: "black and blue spots" of skin. August, 1932: bleeding from gums, pallor. *Examination:* pallor. Gums swollen, spongy, bleeding. Few petechiæ and ecchymoses.	May 1, 1932: Hemoglobin, 75%. R.B.C., 3.86. W.B.C., 8400. P., 70; L., 28; E., 2. August-September, 1932: Hemoglobin, 50%. R.B.C., 2.50. W.B.C., 6000 to 10,000. Platelets: rare. Red blood cells: achromia +; anisocytosis +; poikilocytosis +; polychromatophilia +. Differential count (author): mature N., 23%; metamyelocytes, 2%; myelocytes, 2%; myeloblasts, 48%; lymphocytes, 23%; monocytes, 2%.

Clinical Diagnoses.

Original: ? Vincent's angina; ? purpura hemorrhagica; ? agranulocytosis.
Author's: aleukemic myelosis.

Bone-marrow Biopsy.	*Uterine Tumor.*
Smear: ratio of W.B.C. to nucleated R.B.C., 1 to 0.04. Differential count: mature N., 0; metamyelocytes, 3.7%; myelocytes, 0.3%; myeloblasts, 86%; histiocytes, 10%. Most of the myeloblasts were oxidase positive. *Fig. 6.*—Photomicrograph of section of sternal bone marrow. (× 985.) Stuffing of marrow cavity with proliferating myeloblasts (*Myb*). Rare erythroblastic cell or megakaryocyte. *Diagnosis:* acute myelosis.	Re-study showed growing invasive neoplasm of primitive cells with nucleoli and *oxidase* and *dopa* positive. *Fig. 7.*—Photomicrograph of section of tumor of uterus removed at operation. (× 985.) Dopa stain. Note the neoplastic process composed of embryonic cells (myeloblasts), many of them showing a positive "dopa" reaction. *Postmortem examination:* greenish tumors of gall bladder and about the left ureter; numerous enlarged lymph nodes; bone marrow involved throughout. Tumors, lymph nodes, bone marrow all stuffed with rapidly proliferating myeloblasts, almost all oxidase positive.

Final Diagnosis.

Myelosarcoma (chloroma); metastases (aleukemic myelosis).

12. Sylvia W. B.I.H. 23483. *Pre-biopsy diagnosis:* ? Banti's disease; ? chronic myelosis. *Biopsy diagnosis:* ? myelosis. *Final diagnosis:* ? Banti's disease. A girl, aged 19, entered the hospital on March 17, 1932, complaining of easy bruising for several years, and of two severe hematemeses occurring in June, 1931, and January, 1932. *Examination* disclosed moderate pallor and a very large spleen extending upward to the axilla and downward to the pelvic brim. The *blood:* hemoglobin, 62%; R.B.C., 3,700,000; W.B.C., 2500; platelets, 170,000. Differential count: neutrophils, 79% (19% band forms); L., 15%; M., 6%. Quantitative bilirubin, 0.94 mg. per 100 cc. Roentgen rays of bones negative. B.M.R. normal. *Interpretation:* splenomegaly plus evidence of bone-marrow "destruction;" ? aleukemic myelosis; ? Hodgkin's disease; ? Banti's disease (hematemeses). *Bone-marrow biopsy:* hyperplastic marrow with abnormal islands of immature leukopoietic cells containing myeloblasts and histiocytes. Differential count of the W.B.C.: mature neutrophils, 3.3%; metamyelocytes, 34.3%; myelocytes, 18.7%; myeloblasts,

Table 5.—(Case M. Z.)

Clinical Findings.	*Blood Findings.*
History: male, aged 2. Spontaneous ecchymoses 6 months. Increasing pallor 6 months. Swelling of gums 4 mos.	Hemoglobin, 56%. R.B.C., 3.07. W.B.C., 5300. Platelets, 24,000. Bleeding time, 15 minutes. Reticulocytes, 7.4%.
Examination: marked pallor. Ecchymotic spots. Generalized lymphadenopathy. Spleen palpable 2 fingers. Liver just palpable.	Red blood cells: achromia, 0; anisocytosis −; polychromatophilia −; average diameter, 6.95 micra. Differential count: N., 1%; L., 59%; M., 39%; B., 1% (2% ? lymphoblasts).

Clinical Diagnosis.

Obscure anemia.

Bone-marrow Biopsy.	*Further Findings.*
Smears: ratio of nucleated R.B.C. to W.B.C., 0.4 to 1. Granulocytic cells, 47.8%. Lymphoblasts, 43.2% (5 mitotic figures).	*Lymph-node biopsy:* proliferation of lymphoblasts destroying normal architecture of lymph node and invading the capsule.
Sections: infiltration of lymphoblasts and lymphocytes throughout marrow cavity.	*Postmortem:* generalized lymph-node enlargement. Most nodes showed "toxic" necrosis of germinal centers. One node showed stuffing with lymphoblasts.
Fig. 8.—Photomicrograph of section of bone marrow. (× 985.) Note the large number of lymphoblasts (*Lyb*) and lymphocytes (*Ly*) infiltrating the marrow tissue.	
Diagnosis: ? lymphatic leukemia; ? lymphosarcomatosis.	

Final Diagnosis.

Subacute aleukemic lymphadenosis.

17.5%; histiocytes, 12.3%. *Diagnosis:* ? aleukemic myelosis; ? Hodgkin's disease. *Course:* Marked regression in the size of the spleen occurred after 4 Roentgen ray treatments directed over that organ, the spleen at one time retreating under the left costal margin. The patient has since remained well, although she continues to present slight splenomegaly, slight anemia and leukopenia. The diagnosis still remains in doubt.

13. MORRIS Z. B.I.H. 8654 and 9446. *Pre-biopsy diagnosis:* obscure anemia; ? bone-marrow invasion. *Biopsy diagnosis:* lymphoid proliferation in bone marrow; ? lymphosarcoma; ? lymphatic leukemia. *Final diagnosis:* ? lymphosarcomatosis; ? lymphatic leukemia (Table 5).

14. ELLEN O'C. B.I.H. 22702. *Pre-biopsy diagnosis:* pernicious anemia; ? macrocytic anemia of other type. *Biopsy diagnosis:* hypoplasia of bone marrow, ? arteriosclerotic or senile. *Final diagnosis:* hypoplastic anemia, probably arteriosclerotic (Table 6).

TABLE 6.—(CASE ELLEN O'C.)

Clinical Findings.	*Blood Findings.*
History: female, aged 66. Weakness 1 year, increasing recently; loss of 10 pounds in weight; increasing pallor.	Hemoglobin, 68%.
Examination: "pepper-and-salt" hair; tongue smooth at the edges; finger nails flattened. (No other positive findings.)	R.B.C., 2.78.
Gastric analysis: no free hydrochloric acid after injection of histamin.	W.B.C., 7800.
Icterus index, 6. Bilirubin, 0.61 mg. per 100 cc.	Platelets, 354,000.
	Mean corpuscular volume, 123.
	Red blood cells: no achromia, macrocytosis. Av. diameter, 7.9 micra.
	Differential count: N., 26.5%; L., 62.5%; M., 2%; E., 8%; B., 1%.

Clinical Diagnosis.

Pernicious anemia.

Bone-marrow Biopsy.	*Course.*
Sections: generalized increase in fat cells; no megaloblasts seen; sclerosis of marrow vessels.	Large daily doses of parenteral liver extract without reticulocyte or red blood cell response. No response to large doses of iron. Patient has remained in about the same condition (8 months).
Fig. 9.—Photomicrograph of section of bone marrow. (× 870.) Note the marked increase in number of fat cells (sternal marrow). At the right is seen an arteriole, showing evidences of sclerosis.	

Diagnosis:

Hypoplasia of marrow, probably arteriosclerotic.

15. RUTH R. Seen with Drs. L. Blacklow and E. W. Small at Waltham Hospital. *Pre-biopsy diagnosis:* ? pernicious anemia; ? lymphosarcomatosis; ? aleukemic leukosis. *Biopsy diagnosis:* subacute (aleukemic) myelosis. *Final diagnosis:* subacute myelosis (Table 7).

16. EVA S. Seen with Dr. R. F. Bicknell at the Lynn Hospital. *Pre-biopsy diagnosis:* aplastic anemia. *Biopsy diagnosis:* lymphosarcoma invading bone marrow. *Final diagnosis:* lymphosarcoma with metastases causing "myelophthisic anemia" (Table 8).

TABLE 7.—(CASE R. R.)

Clinical Findings.

History: female, aged 40. Weakness 18 months, increasing. Sore tongue 6 weeks. Paresthesias 6 weeks. Loss of weight.
Examination: Extreme pallor. (Tongue normal; spleen not felt; lymph nodes not felt; vibratory sensation normal.)
Gastric analysis: no free hydrochloric acid (histamin not given).
Icterus index, 6.

Blood Findings.

Hemoglobin, 35 to 16%.
R.B.C., 1.90 to 750,000.
W.B.C., 4000 to 2200.
Platelets, 150,000.
Mean corpuscular volume, 115.
Red blood cells: achromia absent; many macrocytes; average diameter, 7.88 micra.
Differential count: N., 36.5%; L., 39%; M., 25%. (No abnormal white cells seen.)

Clinical Diagnosis.

? Pernicious anemia.
? Lymphosarcoma with involvement of the bone marrow.
? Aleukemic leukosis.

Bone-marrow Biopsy.

Smear: ratio of W.B.C. to nucleated R.B.C., 1 to 0.1.
Differential count: mature N., 0.4%; metamyelocytes, 1.2%; myelocytes, 3.2%; pre-myelocytes, 7.6%; myeloblasts, 69%; histiocytes, 17.6%; eosinophils, 1.6%.
Section: extremely cellular marrow, normal tissue replaced by proliferating leukopoietic cells, oxidase positive.
Fig. 10.—Photomicrograph of section of bone marrow. (× 985.) Note the crowding of the marrow with granulocytic cells, myeloblasts (*Mbl.*) and myelocytes (*Mye*), myelocytes predominating.
Diagnosis: subacute myelosis (aleukemic myelogenous leukemia).

Postmortem Examination.

Myeloblastic proliferation, patchy in type with overcrowding of normal marrow tissue.

Final Diagnosis.

Subacute aleukemic myelosis.

17. NELLO L. Seen with Dr. Smith at the Quincy Municipal Hospital. *Pre-biopsy diagnosis:* ? aplastic anemia; ? lymphosarcomatosis; ? aleukemic leukosis. *Biopsy diagnosis:* aplastic anemia. *Final diagnosis:* aplastic anemia.

An unemployed boy, aged 17, was well until onset of severe epistaxes, beginning in January, 1934. He became progressively paler. At no time had he come in close contact with chemicals. *Examination* in March, 1934, showed, besides the pallor, a few ecchymotic spots on the legs and arms. There was no lymph-node or splenic enlargement and no icterus. *Blood studies:* hemoglobin, 35 to 25%; R.B.C., 1,190,000 to 1,060,000; W.B.C., 2000 to 1000; platelets, 100,000; reticulocytes, 1%; differential count of

the white cells: N., 40%; L., 54%; M., 6%. He was transfused several times without relief. *Interpretation:* probably aplastic anemia—no etiologic agent discernible; ? lymphosarcoma invading the bone marrow; ? atypical aleukemic leukosis; ? osteosclerotic marrow. *Bone-marrow biopsy:* almost complete replacement of entire sternal bone marrow with fat cells. A few tiny islands of red cell and white cell growth present. *Diagnosis:* aplastic anemia. *Course:* Death after repeated transfusions.

TABLE 8.—(CASE E. S.)

Clinical Findings.	*Blood Findings.*
History: female, aged 51, housewife. Fatigue and weakness increasing during 2 years. Extreme weakness and pallor 3 months.	Hemoglobin, 22%.
	R.B.C., 1.00.
	W.B.C., 4500.
	Platelets, much diminished.
Examination: Extreme pallor. (Tongue normal, no icterus, no lymphadenopathy, no splenomegaly, no abdominal or other masses.) Several petechiæ of skin and mucous membranes.	Reticulocytes, 0.6%.
	Average R.B.C. diameter, 7.6 micra.
	Red blood cells: no achromia; anisocytosis +; poikilocytosis +; polychromatophilia 0.
Laboratory findings: gastric analysis; no free HCl. Icterus index, 7. Stools, urine, etc., all negative.	Differential count: N., 32%; L., 62%; M., 4%. (No abnormal or young cells.)

Clinical Diagnosis.

Aplastic anemia.

Bone-marrow Biopsy.	*Course.*
Smears showed few cells.	No relief with large doses of iron, large amounts of liver extract parenterally, multiple transfusions.
Sections: hypoplastic marrow in most sections. One area of cellular hyperplasia consisting of uniform cells with many mitoses pushing aside and infiltrating normal marrow tissue.	
Figs. 11 and 12.—Low- (× 300) and high- (× 1000) power photomicrographs of section of bone marrow. Note the mass of proliferating cells infiltrating and invading the normal marrow tissue (*NM*). The proliferating cells are identified as lymphoblasts (*Lbl*). A mitotic figure is seen (*Mi*).	

Diagnosis: lymphosarcoma invading bone marrow, resulting in "myelophthisic" anemia.

18. RICHARD S. Boston Disp. 295953. *Pre-biopsy diagnoses:* splenomegaly ? cause; ? thrombocytopenic purpura; ? Banti's disease; ? aleukemic myelosis. *Biopsy diagnosis:* chronic myelosis.

A school boy, aged 14, had been troubled with black and blue spots since the age of 3 months and had had numerous examinations, always with negative results until July, 1934. At this time he complained of constant fatigue. *Examination* showed a large spleen extending to the umbilicus

and a few slightly enlarged lymph nodes. *Blood studies:* hemoglobin, 77%; R.B.C., 4,700,000; W.B.C., 3100; platelets, 175,000. Differential count: neutrophils, 50% ("band" forms, 6; myelocytes, 2); lymphocytes, 46%; monocytes, 2%; eosinophils, 2%; bleeding time, 3 minutes; clotting time, 5 minutes. All other clinical and laboratory examinations were negative. *Diagnosis:* splenomegaly ? cause. History of ecchymoses and low platelet count suggestive of thrombocytopenic purpura. Spleen too large and white blood cell count too low for this condition. Banti's disease and aleukemic myelosis most likely. *Bone-marrow biopsy:* hyperplastic marrow with marked increase in activity of leukopoietic tissue; islands of myeloblasts. *Diagnosis:* chronic myelosis. The patient is being followed.

Discussion. 1. *The "Blood" Diseases in Reality Diseases of the Blood-forming Organs.* Until very recently, abnormalities in the red blood cells, white blood cells and blood platelets were uniformly spoken of as "diseases of the blood," "disorders of the blood," the "blood" diseases and the "blood dyscrasias." Emphasis was thus placed upon the changes which were found in the numerical and morphologic characteristics of the cells in the peripheral blood. Hematology was thus for many years a "peripheral" study, in which little note was taken of the fundamental changes in the various blood-forming organs.* Curiously enough, it was the study of the blood picture in various infectious diseases, chiefly by Arneth and Schilling, which brought home the fact to many that an increase in immature granulocytes ("shift to the left") was dependent upon "regenerative" activity of the bone marrow, with resultant changes in the peripheral blood. Study of the pathologic changes occurring in pernicious anemia had shown that the bone marrow was probably implicated.

It was furthermore becoming rapidly apparent that the blood picture might not be the final word in many diverse conditions, and that in certain instances it might even be misleading. The extremely variable blood picture in apparently identical cases of leukosis, the identical blood picture of many widely different disorders (hypoplastic anemia, pernicious anemia, certain cases of Hodgkin's disease, lymphosarcoma, etc.) served to bring this out forcibly. The "release" factor appeared to be as important in the production of the blood picture as did the actual formation and destruction of the blood cells, as could be seen from the study of the bone marrow in agranulocytosis, pernicious anemia and primary hypochromic anemia. The term "blood diseases" has thus gradually become modified to that of "diseases of the blood-forming organs." This should make profitable careful study of the various sites of blood formation in every instance in which the peripheral blood cells show marked disturbance either numerically or morphologically. In most instances, study of the marrow alone should provide the necessary information, although in certain cases biopsy

* It is related of Türck, a famous hematologist of 1880–1890, that when questioned concerning the pathology of a certain "blood" disease, he was offended, drew himself up, and said, "Sir, I am a peripheral hematologist."

of an accessible lymph node is even of greater importance. Correlation of the marrow picture with that of the peripheral blood should result in a better understanding of the physiologic pathology of the various hematologic disorders, so much so that after a certain number of these conditions have been studied, the blood picture alone will usually, by analogy, reveal the state of the marrow. With the gradual development of this fundamental knowledge, the science of hematology should certainly become more "central" than "peripheral" in nature.

2. *The Diagnostic Value of the Bone-marrow Biopsy.* The bone-marrow biopsy, in the above-reported series of cases, has proved of greatest value in the diagnosis of obscure cases of anemia. Many cases presenting anemia as an outstanding symptom fail to present sufficient findings either clinically or hematologically, to warrant an exact diagnosis. This is particularly true in the cases of aleukemic leukosis, of which a number have been presented above. The majority of cases of "leukemia" (leukosis) have, in the author's experience, been associated with a normal or low white cell count, and not with a high white cell count, as is the ordinary teaching. Many of these cases have been misdiagnosed clinically and hematologically. Thus, if a large spleen is present, Banti's disease, or splenic anemia, is usually diagnosed; if the anemia is of the macrocytic type, pernicious anemia is the diagnosis; if petechiæ and ecchymoses are present, purpura hemorrhagica is considered; and if there is a marked leukopenia with but few adult neutrophils, the diagnosis of agranulocytosis is almost always made.

It should be remembered that the leukotic process is composed of primitive, rapidly growing cells which tend to invade normal blood-forming tissue and thus prevent normal blood formation. In the bone marrow, this process (whether myeloid, lymphoid or monocytic) results in impaired formation of red cells, white cells and platelets. This results hematologically in anemia, leukopenia and thrombocytopenia. This triad should always, therefore, suggest bone-marrow "destruction." Usually due to a leukemic proliferation, it may be due to invasion by lymphosarcoma, myelosarcoma (chloroma) or other metastatic malignancy. Careful study of the peripheral blood will usually show, in the leukotic cases, either myeloblasts, lymphoblasts or histiocytes; certain cases, however, do not show these changes. In any event, it is in these obscure cases of anemia associated with leukopenia and thrombocytopenia that the bone-marrow biopsy has been most helpful in the formation of an exact diagnosis, and has demonstrated that even with an extremely cellular marrow, the peripheral blood itself may be almost devoid of cells. The definite diagnosis of leukosis (myelosis, lymphadenosis, reticulosis) has been of great value in ruling out Banti's disease, splenic anemia, pernicious anemia in certain instances, agranulocytosis, purpura hemorrhagica and aplastic anemia. It is

probable that many cases of "agranulocytosis" which have failed to benefit by therapy with nucleic acid derivatives are in reality instances of aleukemic leukosis. The same is probably true of certain cases called "purpura hæmorrhagica." Those cases of "pernicious anemia" which fail to respond to active therapy with the various potent extracts of liver usually turn out to be instances of leukosis. The diagnosis of "aplastic anemia" and "hypoplastic anemia" should for the same reason be suspected.

3. *Value of the Bone-marrow Biopsy in Further Studies.* As noted above, it is necessary to understand blood pictures from the standpoint of their fundamental physiologic background. The bone-marrow biopsy thus becomes a tool in the further study of cases of anemia. The use of the biopsy in the study of pernicious anemia, both before, during and after treatment, has been commented upon. It has been of help in understanding the mechanism of the action of liver extract, etc., upon the hyperplastic, megaloblastic marrow of the disease. With liver extract, there is gradual diminution in the apparently futile hyperplastic formation of embryonic cells and increase in the normal erythronormoblastic type of blood cell formation. The biopsy has already proved useful in the study of primary hypochromic anemia[1,25] and of great interest in the study of Hodgkin's disease. Studies of the marrow in agranulocytosis have shown that in certain instances there is marked hypoplasia of myeloblastic tissue and that in other instances, the reverse is true. From these findings, Beck[27] has recently speculated that certain cases of agranulocytosis are dependent upon FitzHugh and Krumbhaar's[28] lack of a "maturation" factor and others upon the absence of a chemotactic factor. The chief value of the marrow biopsy must remain, however, in its capacity as an aid in the diagnosis of obscure hematologic conditions. It should be pointed out that it is of great advantage that the hematologist be, as far as possible, his own clinician, clinical pathologist and pathologist. In these studies, the author studied each case clinically, made the blood studies, performed the bone-marrow biopsy, and then studied the marrow smears and sections.

Summary. The blood picture is the end result of many complex factors which have to do with the growth, destruction and liberation of the blood cells from the various hematopoietic organs. Although the peripheral blood usually reflects more or less accurately the condition of the blood-forming organs, it is certain that greatly diverse blood pictures may be present in identical pathologic processes. Conversely, identical blood pictures may be associated with fundamentally different disorders. It becomes important, therefore, to study what is "behind" the blood picture, *i. e.*, in the hematopoietic organs. The bone marrow, as the chief blood-forming organ, must deserve greatest consideration, since most of

the so-called "blood diseases" either originate there or are associated with various abnormalities of growth within its confines.

Biopsy of the sternal bone marrow with a small trephine was performed in about 125 cases of diseases of the blood-forming organs. The criteria for cellular diagnosis, together with the findings in the miscellaneous group of diseases, are briefly discussed, and the diagnostic implications considered.

Many cases presenting obscure anemia are not susceptible of ready diagnosis, even after prolonged clinical and laboratory investigations have been made. The marrow biopsy has proved of greatest value in the diagnosis of these difficult cases. Particularly has it demonstrated that many cases of so-called Banti's disease, splenic anemia, agranulocytosis, aplastic anemia and pernicious anemia are in reality, instances of aleukemic leukosis. Anemia, leukopenia and thrombocytopenia are a triad of laboratory findings which point to a "destructive" ("myelophthisic") process in the marrow which is usually "leukemic" in type. Cases illustrating the diagnostic value of the bone-marrow biopsy are briefly described.

Although its chief function is diagnostic, the biopsy has proven of great value as well in appreciation of the "central" character of the blood picture. This has helped greatly in the understanding of the formation of blood pictures in various pathologic conditions.

REFERENCES.

1. Dameshek, W.: Am. J. Med. Sci., **182**, 520, 1931.
2. Fitz-Hugh, T., Jr., and Krumbhaar, E. B.: Ibid., **183**, 104, 1932.
3. Ghedini, G.: Clin. med. ital., **47**, 724, 1908; Wien. klin. Wchnschr., **23**, 1840, 1910; **24**, 284, 1911.
4. Wolff, A.: Deutsch. med. Wchnschr., **29**, 165, 1903.
5. Spuler, A., and Schittenhelm, A.: Deutsch. Arch. f. Klin. Med., **109**, 1, 1913.
6. Zadek, I.: Schweiz. med. Wchnschr., **51**, 1087, 1921.
7. Morris, L. M., and Falconer, E. H.: Arch. Int. Med., **30**, 485, 490, 1922.
8. Seyfarth, C.: Deutsch. med. Wchnschr., **49**, 180, 1923.
9. Weiner, W., and Kaznelson, P.: Fol. hæmatol., **32**, 233, 1926.
10. Escudero, P., and Varela, M. E.: Semana méd., **33**, 701, 1926.
11. Peabody, F. W.: Am. J. Path., **3**, 179, 1927.
12. Arinkin, M. I.: Fol. hæmatol., **38**, 233, 1929.
13. Arjeff, M. J.: Ibid., **45**, 55, 1931.
14. Tuschinsky, M. D., and Kotlarenko, B. N.: Ibid., **46**, 235, 1932.
15. Tempka, T., and Braun, B.: Ibid., **48**, 355, 1932.
16. Isaacs, R.: Ibid., **40**, 395, 1930.
17. Pokrowsky, W. I.: Ibid., **39**, 265, 1930.
18. Barta, I.: Ibid., **50**, 287, 1933.
19. Nordensen, N. G.: Hygeia (Scand.), **96**, 193, 1934; Abstract, J. Am. Med. Assn., **102**, 2154, 1934.
20. Kossirsky, J. A.: Arch. f. Schiffs u. Tropen-Hyg., **37**, 496, 1933.
21. Spartaco, R. A.: Minerva med., **1**, 319, 1932.
22. Custer, R. P.: Am. J. Med. Sci., **185**, 617, 1933.
23. Escudero, P., and Varela, M. E.: Hæmatologica, II. Rec., **3**, 65, 1932.
24. Custer, R. P.: J. Lab. and Clin. Med., **17**, 951, 1932. Custer, R. P., and Ahlfeldt, F. E.: Ibid., p. 960.
25. Kaznelson, P., Reimann, F., and Weiner, W.: Klin. Wchnschr., **8**, 1071, 1929.
26. Dameshek, W.: Arch. Int. Med., **46**, 718, 1930; Fol. hæmatol., **49**, 64, 1933.
27. Beck, R. C.: Arch. Int. Med., **52**, 239, 1933.
28. FitzHugh, T., Jr., and Krumbhaar, E. B.: Am. J. Med. Sci., **183**, 104, 1932.

(Titles have been omitted for sake of brevity.)

SYSTEMATIC VARIATION IN THE HUMAN MENSTRUAL INTERVAL.*

By Oscar W. Richards, Ph.D.,
NEW HAVEN, CONN.

(From the Osborn Zoölogical Laboratory, Yale University.)

The interval between the menstrual periods is not of constant length for many women and recent studies show that the 28-day lunar cycle type is found less frequently as more accurate information becomes available. Pratt *et al.* (1929) emphasize the variability of the menstrual interval and Geist (1930) and King (1926) show objectively the variation that may be found when an accurate record is kept of the periods of women who had previously reported themselves to be regular. Memory for time is poor and suitable data for statistical analysis require the making of a continuous written record. Any analysis of the data accumulated in most clinics would give inaccurate results for this reason. Papanicolaou (1933) has reviewed much of the literature in this field and the variability of menstruation as this function starts is shown by the study of Engle and Schelesnyak (1934).

The clinician and the endocrinologist may wish to know how much variation may be expected in the menstrual intervals of the individual as well as the variation between different women. The statistically inclined person will wish to know in addition how significant any variation found is, or, whether the variations found are those of chance fluctuation. Few of the published papers contain adequate data for the answer of these questions because the observations on different women are averaged together, or are too few to permit the computation of the extent of the variation.

An analysis of the variation in the menstrual interval must be made on a long record of the same individual. Two such records are available for a little more than 9 and 12 years respectively. One individual kept marked yearly calendars (I) and the other a fairly complete diary (IV). The records are nearly complete and believed to be accurate. In addition to these long records the length of the interval, its variation, the age of the subject and length of the record is given in Table 1 for 2 unreported subjects and for 9 of the subjects from King (1926).[1] Subject II is a secretary, III a graduate student and the activities of Subjects I and IV are given in Table 4.

The mean length of the interval is shown in Table 1 to vary

* Interval, as here used, is the number of days from the first day of one menstrual period to the first day of the next period.

[1] Part of the computations were made by Miss Francis Kuchler as a problem in the author's course on the Analysis of Biological Data.

from 24.8 to 34.3 days for these 13 women. The frequency of the intervals for the two longer records are given in Table 2. The variation of the periods for a given subject is measured by the standard deviation (σ) of the periods.[1] Table 1 shows this variation to vary from 1 to 4.8 days for these women. Another convenient index of the variation found in a single record is the coefficient of variation (*c.v.*) which expresses the standard deviation as a percentage of the mean. Subject J has the greatest variation of 14% and H the least variation of 4%. A variation from the mean time of 67% of the standard (0.67σ) would be expected in about one of every two periods, a variation from the mean equal to the number of days in the standard deviation would be expected to occur in about one of every three periods and a deviation from the mean of twice the number of days of the standard deviation would be expected only about 5 times in 100 periods. Such a variation of 2σ, or a greater variation, would usually be taken to show some disturbance beyond that usually occurring in the menstrual rhythm. For most of the persons reported in Table 1 a variation of 2 days would be expected about once in every 3 periods and would not be statistically unusual. However for Subjects II and J a variation of 5 days from the mean period would not be unusual and a deviation of 10 days would be the least that would be statistically significant. The former enjoys normal health and activity. Similar measurement from many different women would be necessary to establish norms for clinical use and these figures are given only to show the variation actually measured in 13 women living in average or superior economic status.

TABLE 1.—GENERAL INFORMATION, MEAN AND VARIATION OF MENSTRUAL INTERVALS.

Subject:	I.	II.	III.	IV.	A.	B.	C.	D.	E.	F.	G.	H.	J.
Age* . . .	21	26	30	23	30	29	21	23	13.5	35	27	33	27
No. of years .	12+	2−	3−	9+	9	7	8	5	5	3	7	3	4
No. of periods (N) . .	134	22	29	110	104	94	63	48	47	29	25	22	21
Mean in days	26.0	32.2	29.2	24.8	28.4	25.3	26.2	28.9	28.7	25.2	28.3	26.8	34.3
σ in days .	2.3	4.8	2.5	1.7	2.2	1.8	1.7	1.7	1.7	1.5	2.4	1.0	4.8
c.v. % . .	9	11	9	7	8	7	6	6	6	6	8	4	14

The computations for subjects A to J based on data from King (1926).
* At the beginning of the record.

TABLE 2.—FREQUENCY OF MENSTRUAL INTERVALS FOR THE TWO LONGER RECORDS.

Days:	18.	20.	21.	22.	23.	24.	25.	26.	27.	28.	29.	30.	31.	32.	33.	35.
Subject I	1	..	3	4	8	16	18	39	17	15	4	5	1	1	1	1
Subject IV	..	1	4	3	10	22	30	18	6	4	2	..	..	..	..	..

[1] When x is any one of N observations the mean, $M = \Sigma x/N$; the standard deviation, $\sigma = \sqrt{\frac{\Sigma(x - M)^2}{N}}$; and the coefficient of variation, $c.v. = 100\sigma/M$.

The mean menstrual interval and its observed variation are slightly different for different women and we may next inquire whether these differences are statistically significant. The greatest difference of 9.5 days is found between the average intervals of Subjects IV and J. The significance of this variation must be evaluated in terms of the variation of both subjects and is obtained as the standard error of the difference,[1] which is 1.06 days. The ratio of the deviation to its standard error is 9.5/1.06 or about 9, and the normal probability table indicates that there is less than one chance in 10^{12} of this difference being other than a statistically significant one. This is an extreme case of a difference obvious even without statistical treatment. A less extreme case would be the difference of 0.9 day between subjects B and C which is only 3 times the standard error of the difference and the probability table shows that this difference would be expected only once in about 370 cases. In general when the difference is twice the standard error of the difference, or greater, the difference is statistically significant and may be important in the clinic. When many periods are available the variation is more completely known and the standard errors are less. From the information in Table 1, a difference of a day or more between the mean menstrual interval of two women is to be regarded as statistically significant and in different women the humoral control or timing of the menstrual cycle is probably different to at least this extent.

The frequency of the menstrual intervals for Subjects I and IV is given in Table 2. The 18 and 33-day intervals of Subject I were caused by mumps and are not included in the following analysis. The 32 and 35-day intervals preceded pregnancy and support the suggestion of a missed period given by the Hotellings (1932). The 21-day cycle (Papanicolaou, 1933) hardly occurs in either record. The 20 and 27-day intervals in the 10th year of Subject IV were associated with a repair operation, the 22-day interval in the 6th year occurred while traveling and the 22 and 29-day intervals of the 2d year occurred during a rest period from excessive fatigue. The other large variations had no apparent explanation. The variation (σ) of Subjects II, III, G and J is greater than that of Subject I. The ultimate explanation of the nature and control of the menstrual cycle must account for variation of this magnitude. The knowledge of this variation, even from a few cases, may aid the clinician to discover the extent of the variation in other cases and to understand its origin.

[1] The standard error of the difference between two means $= \sqrt{\frac{\sigma_1^2}{N_1} + \frac{\sigma_2^2}{N_2}}$ where σ_1 and σ_2 and N_1 and N_2 are the respective standard deviations and numbers of observations in the two sets of data. The probabilities obtained from the ratios are to be found in the several books or tables on statistical method.

The diary of Subject IV gives the hour of day of the onset of the menses in 9 cases, the average time of which is 9.53 A. M. If two occurrences late in the day are omitted the average is 7.56 A.M. If the observations of more diarists were available, it might be possible to make more precise statistical analyses.

Tinklepaugh[1] has suggested that the weekly rhythm of daily life may influence the monthly menstrual cycle and has supported his view with observations on change of daily weight and on the frequent occurrence of the onset of the menses with respect to the Sunday rest day of the week. Table 3, presenting the days of onset for Subjects I to IV, shows more occurrences near the week end.

TABLE 3.—THE FREQUENCY OF ONSET OF MENSES BY THE DAY OF THE WEEK.

Subject:	I.		II.		IIIA.		IIIB.		IV.	
	No.	%	No.	%	No.	%	No.	%	No.	%
Sunday	20	15	5	23	4	20	6	21	16	15
Monday	15	11	6	27	0	0	2	7	12	11
Tuesday	26	20	5	23	0	0	1	3	22	20
Wednesday	18	13	1	4	0	0	2	7	9	8
Thursday	11	16	3	14	4	20	5	17	18	16
Friday	19	14	0	0	7	35	7	24	15	14
Saturday	14	11	2	9	5	25	6	21	18	16
χ^2	5.01		9.28		16.7		11.60		6.96	
P	0.54		0.17		0.01		0.08		0.33	

Except for slight difference in the length of leap years and from cycles that do not divide into 365 days evenly the proportior of onset days of the menses should be the same for each day of the week over a considerable period of time unless a systematic variation occurred. The Chi-square test[2] is appropriate to test whether the variation found from equal probability is greater than fortuitous variation and whether it supports the hypothesis of Tinklepaugh. From the computed value of Chi-square the probability (P) is obtained from the table of Fisher and when this probability is less than 0.05 the data would be considered to support the hypothesis tested. The values found are all greater than 0.05 and do not support the hypothesis except for IIIA in Table 3. Here the first report showed a very unequal distribution with respect to the day of the week. However, the second report added 9 more menstrual periods of the following year which filled in many of the vacancies of the table, thereby increasing the value of P to above the level of

[1] Based on a personal communication from Dr. O. L. Tinklepaugh of data to be published by him.

[2] When C is the observed frequency and E is the expected frequency $\chi^2 = \Sigma\left[\frac{(C - E)^2}{E}\right]$; the number of degrees of freedom, $n = N - 1$, and P is obtained from the table of χ^2 found in Fisher (1932), Chapter 10.

statistical significance. No change in the life of the subject took place to explain the difference in the 2 years and this indicates the necessity of having data over a considerable period of time in order to make meaningful comparisons. Further data will be necessary to adequately test the interesting suggestion of Tinklepaugh and data gathered on menstrual cycles should include the day of week of onset, or the calendar date, so that they may be examined from this viewpoint.

The year by year plot of the record of Subject I failed to show secular (long time trend) but did suggest a possible seasonal variation. To investigate this all of the data were plotted on a large scale graph so that the mean duration of the periods for each year was superimposed on the 26-day mean for all of the years. The individual deviations were then measured from this common reference value. A midvalue was found for the periods falling within each 10-day period of the year by adding algebraically all of the deviations within this 10-day period and then dividing the sum by the number. The averaging was repeated a second time with a 10-day interval beginning at the center of the previous 10-day intervals. The values obtained were plotted and gave a fairly smooth curve which was then smoothed and adjusted so that the standard deviations of each separate year from this line were least. This insured that the representative curve indicated the systematic variation during the entire record. This method of approximation was quicker and nearly as precise as the usual methods for the isolation of seasonal variation.[1] The final result was the smooth heavy line of Figures 1 and 2.

The mentrual intervals of Subjects I were more irregular during the first half of the year, tended to be longer by about 2 days during the summer months and were a little more than 2 days shorter than the average during the late fall of the year. As the seasonal curve is an average for all of the years it will not represent any one year exactly. Therefore, all of the variation is not to be explained in this manner as is illustrated for 8 years of the record in Figure 1. The years in which the data are incomplete or interrupted with pregnancies are omitted from the figure.

The variance (σ^2) was calculated for each year and the standard variation (σ'^2) for each year was computed in a similar manner, but measuring the deviations from the corresponding point of the curve of seasonal variation rather than from the mean. The ratio (μ) of these values (σ'^2/σ^2) for each year measures the agreement of the menstrual intervals for that year with the seasonal variation. The smaller this ratio the better is the agreement and with very good agreement the ratio would be nearly zero. The lack of complete agreement indicates the amount of variation due to other causes.

[1] For other methods see Rietz (1924) and Richards and Dawson (1927).

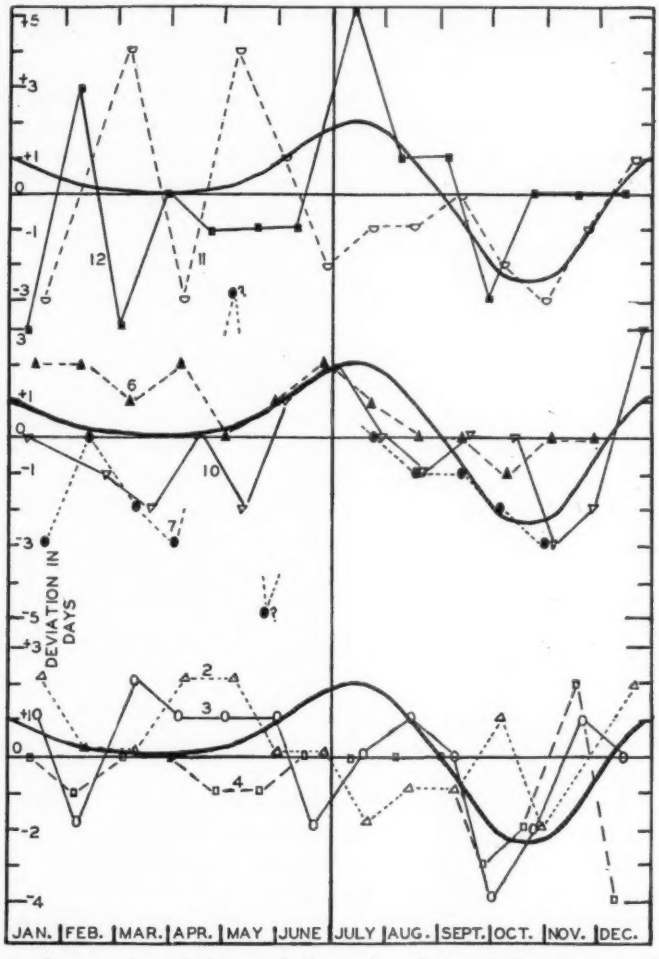


FIG. 1.—Systematic variations and observed variation of the menstrual rhythm of Subject I. The continuous heavy line (repeated in each graph) is the systematic variation and the observed variation is shown by the other lines numbered to correspond with the year in Table 4 (see text).

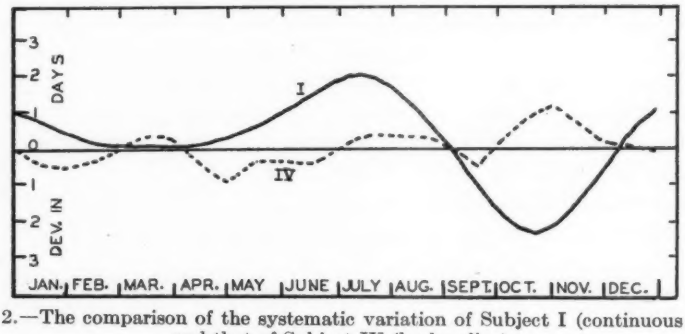


FIG. 2.—The comparison of the systematic variation of Subject I (continuous line) and that of Subject IV (broken line).

The ratios, Table 4, are less than unity for all of the years except the second, fourth and eleventh. The second year is out of phase with the seasonal trend. The seventh year shows good agreement except for the two marked fluctuations due to mumps marked by interrogation points on the graph (Fig. 1). The fourth year was the most uniform as half of the intervals were the same length as the mean and the twelfth year was the most variable especially during the summer months. The deviations of the seventh year may be due to traveling also those of the eleventh year. Except as marked in Table 4 or previously mentioned, the changes in the life of the subject do not throw any further light on the observed variation.

TABLE 4.—ANALYSIS OF THE DATA FOR SEPARATE YEARS.

A. SUBJECT I.

Year:*	S1.	S2.	M3.	H'4.	T6.	V7.	P8.	P9.	H10.	T11.	H12.	
Number	In 8	13	14	14	12	12	7	5	15	14	14	
Mean	24.6	26.1	24.6	28.1	29.5	25.0	27.2	26.5	26.1	25.6	25.7	
σ . .	...	1.71	1.69	1.61	1.43	3.45	2.77	1.85	1.66	1.97	2.39	
σ' . .	...	1.83	1.61	1.81	1.2	1.89	2.08	....	1.54	2.18	2.35	
Ratio μ	...	1.15	0.91	1.30	0.70	0.30	0.56	....	0.86	1.25	0.97	Av. 0.89

B. SUBJECT IV.

Year:*	S2.	S3.	S4.	TTe5.	TTe6.	Te7.	M8.	HP9.	HP10.	
Number .	10	11	11	In 7	15	15	15	7	6	
Mean . .	25.4	24.6	24.8	24.4	24.7	24.3	24.5	25.4	24.1	
σ . . .	2.1	1.99	1.19	1.64	1.25	1.53	0.87	1.52	3.12	
σ'' . . .	1.87	1.73	1.04	1.61	1.23	1.39	0.89	1.27	2.07	
Ratio μ .	0.35	0.76	0.77	0.97	0.97	0.83	1.02	0.67	0.45	Av. 0.77

$\mu = \sigma'^2/\sigma^2$ or σ''^2/σ^2.
$\sigma'' = \sigma'$ less known deviations.
* Activities during the year are keyed as follows: In = incomplete, H = housewife, H' = housewife and also working in library, M = married, S = university student, T = traveling, Te = teaching, V = mumps, P = pregnant.

The general curve of variation is referred to as seasonal variation because that is a convenient descriptive term, but the variation may or may not be related to the seasons of the year. The shorter periods of the fall cannot be attributed solely to light as has been done with some of the lower animals (Wetham, 1933), because the return to average duration occurs when the days are shortest. The longer periods of the summer months may be a result of the higher temperature at that time. There was no change in the habits of the subject during the year that would explain this systematic variation of the menstrual periods.

The record of Subject IV shows no secular trend but does have a smaller cycle of seasonal variation which was isolated by the same method and is shown on Figure 2. Less variation is observed as would be expected since the standard deviation of Subject IV is less than that of Subject I. The curves are quite different with the longer intervals of Subject IV occurring in the late fall at the same time that they were shortest for Subject I. This difference suggests again that the systematic variations are individual differences and

not related to the season of the year. The year by year analysis of the record of Subject IV, Table 4, shows somewhat better agreement than that of Subject I.

Few records of sufficient length for analysis have been published or are available for comparison. There seems to be no such definite variation in the record of Subject A of King's (1926) paper. The number of observations in the other records are too few for detailed study. It will be interesting to know whether there is any evidence of systematic variation in the record of the special case covering 21 years of Papanicolaou (1933).

An adequate study of the variation of the menstrual interval will require accurate and consecutive records made over a considerable period of time for a number of normal women. The number of observations required will depend on the amount of the variation found. This variation must be stated in future published accounts as well as the length of the mean interval to permit close comparisons of the records of different subjects. When the data of many cases are combined from clinical records further analysis is impossible. The frequency of occurrence should be recorded for each day of the week and relevant data from the daily life of the subject should be added.

Summary. The mean length and variation of the menstrual interval is here given for 4 cases not previously published and for 9 cases from the literature. Some of the women showed a variation nearly 5 times greater than others within this small group. From the experience of this group of women a variation of 1 to 5 days may be expected and variations of from 2 to 10 days, depending on the variation of the individual case, indicate a definite departure from the normal variation. A variation of about 1 day in the mean intervals between 2 women is statistically significant and shows that there are marked individual differences in the menstrual rhythm. A systematic variation was found in the long records of two of the subjects. One menstruated less frequently in summer and more frequently in the late fall of the year. This systematic variation was followed more closely after interruption by pregnancy. The other subject menstruated more frequently in late spring and less frequently in late fall. The necessary formulæ of this kind of analysis are given. Further comparison of the results will have to await the publication of more data for analysis. It is believed that a knowledge of the individual variations in the menstrual rhythm will be of use to the clinician and will aid the study of the control of the female sexual cycle by the endocrine glands.

BIBLIOGRAPHY.

Engle, E. T., and Schelesnyak, M. C.: First Menstruation and Subsequent Menstrual Cycles of Pubertal Girls, Human Biol., **6**, 641, 1934.

Fisher, R. A.: Statistical Methods for Research Workers, 4th ed., Edinburgh, Oliver & Boyd, p. 307, 1932.

Geist, S. H.: The Variability of the Menstrual Rhythm and Character, Am. J. Obst. and Gynec., **20**, 320, 1930.

Hotelling, H., and Hotelling, F.: A New Analysis of the Duration of Pregnancy Data, Ibid., **23**, 643, 1932.

King, J. L.: Menstrual Records and Vaginal Smears in a Selected Group of Normal Women. Contrib. to Embryol., No. 95, Carnegie Inst. of Washington, **18**, 81, 1926.

Papanicolaou, G. N.: The Sexual Cycle in the Human Female as Revealed by Vaginal Smears, Am. J. Anat., **52**, 519, 1933.

Pratt, J. P., Allen, E., Newell, Q. U., and Bland, L. J.: Human Ova From Uterine Tubes, J. Am. Med. Assn., **93**, 834, 1929.

Richards, O. W., and Dawson, J. A.: The Analysis of the Division Rate of Ciliates, J. Gen. Physiol., **10**, 853, 1927.

Rietz, H. L.: Handbook of Mathematical Statistics, Boston, Houghton, Mifflin Co., p. 221, 1924.

Wetham, E. O.: Factors Modifying Egg Production With Special Reference to Seasonal Changes, J. Agric. Sci., **23**, 383, 1933.

THE DAILY REQUIREMENT IN HUMAN HYPOTHYROIDISM OF PURIFIED HUMAN THYROID HORMONE AT VARIOUS METABOLIC LEVELS.

A Comparison Between Spontaneous Myxedema and Cachexia Strumipriva.

By Eugene C. Eppinger, M.D.,
Resident Physician, Peter Bent Brigham Hospital,
and
William T. Salter, M.D.,
Assistant Professor of Medicine, Harvard Medical School,
Boston, Mass.

(From the Medical Clinic of the Peter Bent Brigham Hospital and the Huntington Memorial Hospital of Harvard University.)

Increased clinical interest in removal of the thyroid as a therapeutic measure in circulatory disturbances[1] has extended the necessity of using thyroid preparations for substitution therapy. In a previous communication[2] it was suggested that there existed appreciable differences between individuals with spontaneous and those with surgical hypothyroidism in their responsiveness to thyroid extract. Inasmuch as many such surgically treated patients are on the verge of cardiac decompensation, it is especially important to be able to judge with some accuracy the metabolic level which a given dose of thyroid will cause this type of patient to assume. Conversely, if it is desired to hold a patient at a certain substandard level of caloric turnover, it is necessary to know the daily requirement of thyroid hormone needed in such a case. Such knowledge offers an added safeguard to the sudden overburdening of cardiac reserve.

From the physiologic standpoint also, it is desirable to know how

far the spontaneous variety of myxedema resembles hypothyroidism produced by total thyroidectomy. It is the purpose of this paper to report studies of the daily requirement of thyroid hormone in cases of spontaneous and surgical myxedema, respectively, when adjusted to a steady state at various levels of metabolic equilibrium.

Plan of Study. The cases selected for observation were of two sorts. The first class consisted of 2 cases of spontaneous myxedema, one of whom had never been treated and the other of whom had relapsed after withdrawal of medication for 220 days. The second group consisted of 4 cases of typical myxedema following total ablation of the thyroid by Dr. E. C. Cutler.*

Following complete ablation of thyroid tissue the patients' basal metabolic rate was allowed to drop until the symptoms of myxedema became sufficiently severe to necessitate thyroid therapy. At this stage various patients had attained different levels of metabolism in accordance with the well known lack of correlation between basal metabolic rate and the clinical picture. The initial metabolism before treatment varied from −40% to −20% (Table 1). Inasmuch as this paper deals only with maintenance requirements at steady states of metabolism, it was not essential that the metabolic histories run parallel to each other. The presence of myxedema seemed absolutely certain in all these cases because of the invariable finding of clinical symptoms together with striking elevation of the blood cholesterol above the pre-operative level. The subsequent marked response to small amounts of thyroid hormone further validates the diagnosis of hypothyroidism.

TABLE 1.—DAILY CONSUMPTION OF HUMAN THYROID HORMONE AT VARIOUS METABOLIC LEVELS. (EXPRESSED IN MILLIGRAMS OF THYROGLOBULIN IODIN.)

Metabolic rate.	Spontaneous myxedema.				Surgical myxedema.				Spontaneous myxedema,
	Case 1.*		Case 6.†						
	Human.	Desiccated.‡	Human.	Desiccated.‡	Case 2.*	Case 3.*	Case 4.†	Case 5.†	Means and Lerman.‡
+10%	...	0.4							
±0	0.7	...	0.3			0.2	...	0.1	0.4
−10	0.6	0.2	0.2	...	0.2	0.15	0.3	...	0.1
−20	0.3	...	0.1	0.1	0.1	...	0.1	...	0.05
−30	0.1	...	0.05	...	...				
Av. initial B.M.R. before treatment	−40%	...	−40%	...	−25%	−20%	−32%	−26%	

* Treated with thyroglobulin from multiple colloid adenomatous goiter ("non-toxic").
† Treated with thyroglobulin from primary hyperplastic glands ("toxic").
‡ Calculated on the assumption that U.S.P. desiccated thyroid contains 0.2% thyroglobulin iodin.

In order to have a standard and fairly pure source of thyroid hormone, it was decided to use thyroglobulin extracted from human glands. These were obtained fresh after surgical removal and extracted with 0.02 normal sodium hydroxid. From this solution the thyroglobulin was repeatedly precipitated, redissolved and reprecipitated with dilute hydrochloric acid

* We owe to Drs. Cutler and S. A. Levine the opportunity of studying these cases after operation.

at the iso-electric point of the protein (about pH 5). The purity of such a product in terms of other protein has been tested by Dr. Saul Hertz,[3] who found that it evoked antibodies to human thyroglobulin in rabbits, without producing antibodies to human serum albumin or globulin.

The source of the thyroglobulin used was of two sorts, namely primary hyperplastic glands ("toxic") and multiple colloid adenomatous glands ("non-toxic"). These two preparations of thyroglobulin will be referred to in this report as "toxic" thyroglobulin and "non-toxic" thyroglobulin, respectively.

The strength of the medication was gauged quantitatively in terms of total iodin. The experimental justification for total iodin as a measure of thyroid activity has been discussed by Lerman and Salter.[4] These authors have also pointed out the variation in activity of various preparations of desiccated thyroid now on the market, which makes accurate estimation of thyroglobulin *iodin* desirable in quantitative clinical studies.

It is of interest that, when assayed by the method of Harington and Randall,[5] the moiety of iodin apparently present as thyroxin was in the case of the "non-toxic" preparation 30% of the total iodin and in the "toxic" preparation 25% of the total. The use of these two types of human thyroglobulin must be borne in mind in judging the effects to be described.

Clinical Procedure. Determinations of the basal metabolic rate were made daily except Sundays (Benedict-Roth apparatus). In all cases the patients were hospitalized and remained in bed, except for toilet privileges. A preliminary series of determinations was made until a stable metabolic level had been attained. Thereupon, the administration of thyroglobulin was begun in a small daily dose which was continued until metabolic equilibrium had been established at a higher level. The daily dose was then increased and continued until a second plateau had been attained. In this way it was possible to correlate various levels of caloric turnover with the corresponding daily administration of thyroid hormone.

In order to insure ready assimilation of the medication, the iso-electric suspension of undenatured thyroglobulin was each day dissolved with a few drops of dilute aqueous sodium hydroxid and added to 60 cc. of orange juice. This procedure was carried out in all cases except Case 1 (spontaneous myxedema), in which instance the thyroglobulin was not alkalinized. Thompson[7] pointed out that alkalinization of a peptide of thyroxin insures maximal absorption of the drug. This is in all probability due to a simple solubility effect (Lerman and Salter[8]). Inasmuch as Barnes and Bueno[6] have shown that soluble thyroglobulin is rapidly absorbed from the intestine, the lack of alkalinization in the first case probably had no significant influence on the results obtained. The result of better assimilation, in any event, would merely tend to make the response obtained in Case 1 more closely approximate the responses obtained with the other patients.

Metabolic Data. The results of the determinations of metabolic response are presented in Table 1. Only the value attained at each equilibrium level is given, in association with the daily dose of thyroglobulin iodin required to maintain it. As was to be expected,

relatively more thyroid substance was needed to maintain metabolism at higher than at lower levels. By comparing these levels it is possible to calculate the rise in metabolic rate produced by each additional 0.1 mgm. of thyroid iodin given. These values are presented in Table 2, for two ranges of initial metabolic rate (as measured before treatment). For comparison, there are included in certain instances in these tables the metabolic effects attained with Armour's desiccated thyroid extract. Table 1 also gives data recalculated from values for desiccated thyroid given by Means and Lerman[9] in spontaneous myxedema.

TABLE 2.—EFFECTIVENESS OF THYROGLOBULIN IODIN IN ELEVATING BASAL METABOLIC RATE. (THE INDEX SHOWS THE RISE IN METABOLIC LEVEL TO BE EXPECTED PER 0.1 MG. OF IODIN ADMINISTERED DAILY.)

	Range of initial metabolic rate before treatment.	
	Severe myxedema, −40 to −20.	Mild myxedema, −20 to ±0.
Increase in B.M.R. from previous level:		
Spontaneous myxedema:		
Case 1*	6.7	5.6
Case 6† (human thyroglobulin)	19.2	10.0
(desiccated)‡	20.0	
Surgical myxedema:		
Case 2*	....	10.0
Case 3*	....	10.0
Case 4†	5.3	
Case 5†	....	10.0

* Treated with thyroglobulin from multiple colloid adenomatous goiter ("nontoxic").

† Treated with thyroglobulin from primary hyperplastic glands ("toxic").

‡ Calculated on the assumption that U.S.P. desiccated thyroid contains 0.2% thyroglobulin iodin.

It will be noted that the data vary over 50% from the mean, although there are too few values to warrant serious statistical treatment. This variation, we feel, is not due to technical errors but represents rather the random variation to be expected in a series of biologic measurements of this sort. Fortunately, the values for surgical myxedema are in general intermediate between those for our two spontaneous cases. Although more observations are desirable for greater accuracy, the expense of prolonged hospitalization has necessarily limited opportunity for greater exactness.

Discussion. Of special interest is the relative effectiveness of thyroglobulin iodin at different levels of metabolism in the mild and severe stages of spontaneous myxedema. In both of the cases here studied, the response was more marked at lower metabolic levels, in accord with long-established clinical experience. Table 2 offers quantitative evidence of this qualitative observation. It will be observed from Table 2 that the permanent elevation of metabolic rate produced by a daily dose of a 0.1 mgm. of thyroglobulin iodin varied from 19.2 points to 5.6 points above the pre-

ceding stationary level. More specifically, the data may be grouped into (*a*) the mild and (*b*) the severely myxedematous cases.

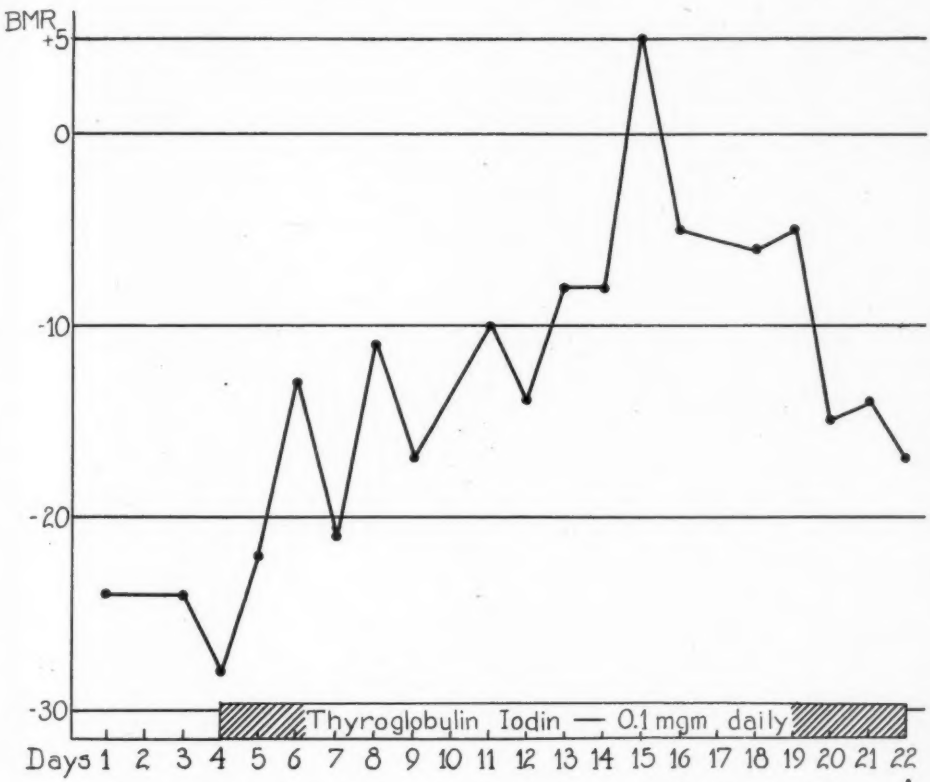


CHART I.—Response of human myxedema (surgical) to human thyroglobulin.

Thus, in the first case treated with "non-toxic" hormone the index for severe stage was 6.7 points per 0.1 mgm. of iodin as against 5.6 points per 0.1 mgm. of iodin in the mild stage. In the second case, treated with "toxic" hormone, the corresponding indices were 19.2 points per 0.1 mgm. of iodin during severe symptoms, as against 10 points when recovery was nearly complete. Whether the discrepancy between the effects of "toxic" and "non-toxic" preparations is due to chance variation or to actual difference in potency cannot be determined from the few cases reported here. Lerman and Salter[8] have presented evidence which indicated no significant difference in the potency of these two preparations of thyroid hormone.

It is of interest that these extremes were found in the cases of spontaneous myxedema. In between these extremes are found the indices determined for the artificial surgical hypothyroidism, which ranged from 10 to 5.3 points per 0.1 mgm. of iodin. There is no

evidence from these figures to indicate that the response of artificial hypothyroidism to purified thyroid hormone shows any significant difference from that of spontaneous myxedema.

Means and Lerman[9] have given average values of thyroid consumption in myxedema at three metabolic levels. These are reproduced in terms of iodin in Table 1. Our values in the 4 cases of surgical myxedema are quite similar. One of our cases of spontaneous myxedema (Case 6) likewise checks closely. Our other spontaneous case (Case 1) however, required nearly twice as much thyroid iodin while myxedema was slowly being relieved for the first time. Subsequently during ambulatory treatment with Armour's extract values approaching the general average were obtained.

In following the metabolic response of these patients while on a constant dose of thyroid hormone, a confusing feature was the tendency to overshoot metabolic equilibrium before settling back to a constant basal metabolic rate. This phenomenon is illustrated for Case 5 by Figure 1. Presumably the explanation lies in general structural and physiologic changes undergone by the organism as it recovers from the myxedematous state. It is conceivable that after maintaining a given metabolic level for many days, the requirement of thyroid hormone at this level may change. There was some evidence to suggest this in Case 1, but rigorous hospital control of the patient over the course of many weeks after recovery was not feasible.

Summary and Conclusions.—The effects of purified human thyroglobulin were studied in 2 cases of spontaneous myxedema and in 4 cases of artificial hypothyroidism surgically produced. These studies compare the responsiveness of myxedematous patients at various metabolic levels to purified human thyroglobulin. The results indicate that there is a fairly characteristic daily requirement of thyroglobulin iodin at any given level of metabolism. No definite discrepancy could be discerned between spontaneous myxedema and hypothyroidism produced by complete ablation of the thyroid gland.

In general, an addition of 0.1 mgm. of thyroglobulin iodin to the daily dose of hormone elevated the basal metabolic rate 10 ± 5 points.

REFERENCES.

1. Blumgart, H. L., Levine, S. A., and Berlin, D. D.: Congestive Heart Failure and Angina Pectoris. The Therapeutic Affect of Thyroidectomy on Patients Without Clinical or Pathological Evidence of Thyroid Toxicity, Arch. Int. Med., **51**, 865, 1933.

2. Eppinger, E. C., and Levine, S. A.: The Medical Care of Patients Following Total Thyroidectomy, J. Am. Med. Assn., **102**, 2076, 1934.

3. Personal communication.

4. Lerman, J., and Salter, W. T.: The Calorigenic Action of Thyroid and Some of Its Constituents, Endocrinology, **18**, 317, 1934.

5. Harington, C. R., and Randall, S. S.: The Chemical Assay of Thyroid Gland, Quart. J. Pharm. and Pharmacol., **2**, 501, 1929.

6. Barnes, B. O., and Bueno, J. G.: Studies on Thyroglobulin. II. Absorption of Thyroglobulin and Related Substances From the Alimentary Canal, Am. J. Physiol., **103**, 570, 1933.

7. Thompson, W. O., Nadler, S. B., Thompson, C. K., and Dickie, L. F. N.: The Effect of Alkali on the Absorption of a Peptide of Thyroxine from the Gastro-intestinal Tract, J. Clin. Invest., **13**, 933, 1934.

8. Lerman, J., and Salter, W. T.: The Metabolic Effects of Human Thyroglobulin and its Proteolytic Cleavage Products. (In press.)

9. Means, J. H., and Lerman, J.: The Symptomatology of Myxœdema: Its Relation to Metabolic Levels, Time Intervals, and Rations of Thyroid, Trans. Assn. Am. Phys., **49**, 214, 1934.

STUDIES OF GALL-BLADDER FUNCTION.

XII. THE COMPOSITION OF "WHITE BILE."*

BY CECILIA RIEGEL, PH.D.,
ASSOCIATE IN SURGICAL RESEARCH,

I. S. RAVDIN, M.D.,
J. WILLIAM WHITE PROFESSOR OF SURGICAL RESEARCH,

CHARLES G. JOHNSTON, M.D.,
HARRIET M. FRAZIER FELLOW IN SURGICAL RESEARCH,

AND

PHILIP J. MORRISON, A.B.,
ASSISTANT IN SURGICAL RESEARCH.

(From the Department of Research Surgery, University of Pennsylvania.)

IN the course of our earlier investigations of gall-bladder function we found that when the bile-free gall bladder of the dog became damaged there occurred a retardation of the rate of water absorption until, finally, instead of fluid being absorbed, fluids poured into the gall-bladder lumen.[5] The fluid which we recovered had all of the physical characteristics of "white bile," or hydrops fluid, and was, as Rous and McMaster[6] have stated, the result of the activity of the mucosal cells lining the lumen of the extrahepatic biliary system. Chemical analysis of this fluid showed it to contain approximately 100 milliequivalents per liter of chlorid, 2.5 to 5 milliequivalents per liter of calcium, and 60 milliequivalents per liter of CO_2. No bile salt was found in these specimens and the amount of cholesterol present was insignificant.

When a damaged biliary system becomes obstructed either in the cystic or common duct, the pent-up bile in the obstructed portion of the biliary tract is gradually diluted by the secretion of the mucosal cells and finally it becomes colorless, the bile pigment being either absorbed or undergoing a change to a colorless type of pigment. Whether an active acute infection is a factor in this

* Aided by a grant from the Josiah Macy, Jr., Foundation.

mechanism, as Aronsohn[1] believes, is as yet controversial. It is, however, important that the mucosal cells of the gall-bladder wall, or the common duct, or both, be damaged.

During our investigations of the gall bladder and liver bile of the human being we were fortunate in securing at operation 15 specimens of hydrops fluid. In every case the cystic duct was found at operation to be occluded so that hepatic bile could not enter the gall bladder. In 2 patients we were able to secure the secretion from the gall bladder over a period of several days subsequent to operation. The study of this material forms the basis of the following report.

There has been a paucity of data on hydrops fluid, or "white bile," in the literature. Winternitz,[8] Elman and Taussig,[3] Bernhard,[2] Aronsohn[1] and Fowweather and Collinson[4] have published data on the chemistry of "white bile," but in each instance the data are limited to a single or, at most, a few observations. In a number of other instances chemical studies have been of a purely qualitative character. In others no chemical data are given. Frequently deductions and generalizations are drawn which are unwarranted from the data the author apparently has had at his disposal.

Results. The original specimens obtained from our patients must be divided into two groups. In the first group (Table 1, 10 specimens), the chlorid concentration varied from 83 to 135 milliequivalents per liter, while the calcium concentrations of this group varied from 3 to 7 milliequivalents per liter. Cholesterol was present in only very small amounts, the highest being 28 mg. per 100 cc. Analysis failed to show the presence of bile salt as determined by the Gregory-Pascoe method. No analyses were made for bile pigment, since the material was colorless.

TABLE 1.—THE COMPOSITION OF "WHITE GALL-BLADDER BILE." LOW-CALCIUM GROUP.

Patient.	Calcium, mEq./L.	Chlorid, mEq./L.	Bile salt, mg./100 cc.	Cholesterol, mg./100 cc.
La.	6	99	0	
Fi.	6	100	0	
McC.	3	83	0	
Ca.	5	93	0	0
Ha.	7	133	0	0
Go.	4	122	0	Less than 5
Ma.	5	119	0	8
Wi.	3	132	0	2–4
Wa.	6	135	0	28
Da.	4	114	0	

In the second group (Table 2, 5 specimens) the material obtained from the gall bladder was sometimes colorless, but other specimens were somewhat milky in appearance, although they were not of the "milch-calcium" type described by Volkmann.[7] The chlorid concentrations in this group varied from 106 to 140. The calcium

concentrations were definitely higher than in Group 1, varying from 11 to 44 milliequivalents per liter, thus containing calcium in concentrations varying from 2 to 8 times the normal serum level. The cholesterol concentrations tended to be on the whole somewhat higher than those found in the first group. No bile salt was found in this group.

TABLE 2.—THE COMPOSITION OF "WHITE GALL-BLADDER BILE." HIGH-CALCIUM GROUP.

Patient.	Calcium, mEq./L.	Chlorid, mEq./L.	Bile salt, mg./100 cc.	Cholesterol, mg./100 cc.
Le.	16	134	Trace	27
Ch.	25	140	0	Fluid 26 Fl. and ppt. 143
Pe.	32	127	0	15
Kr.	44	106	0	
Sc.	11	112	...	52

In Tables 3 and 4 are given the data on 2 patients in whom the gall-bladder secretion free from bile was studied over a period of several days. The data are similar to those reported in Table 1 except that in 1 patient the cholesterol concentrations were, as a rule, higher than those reported in Table 1, and with a single exception higher than those found at any time in the second patient.

TABLE 3.—THE COMPOSITION OF FLUID DRAINED FROM GALL BLADDER DAILY. PATIENT 1.

Date, 1934.	Chlorid, mEq./L.	Calcium, mEq./L	P total, mg./100 cc.	Bile salt, mg./100 cc.	Cholesterol, mg./100 cc.
May 31	103.9	7.3	3.8	0	
June 1	97.9	7.3	3.0	0	
2	107.0	7.5	2.6	0	12.4
3	102.2	7.4	3.6	0	
5	102.2	6.8	2.9	0	30.8
6	101.5	6.2	3.2	0	
7	111.8	6.3	3.0	0	
8	120.9	5.0	2.5	0	
9	111.6	4.5	4.0	0	20.0
10	116.4	4.5	2.3	0	36.5
11	112.8	4.3	2.6	0	13.2

TABLE 4.—THE COMPOSITION OF FLUID DRAINED FROM GALL-BLADDER DAILY. PATIENT 2.

Date 1934.	Chlorid, mEq./L.	Calcium, mEq./L.	P total, mg./100 cc.	Bile salt, mg./100 cc.	Cholesterol, mg./100 cc.
Sept. 21	119.0	4.4	1.20	0	5.8
22	110.6	4.0	0.85	0	8.3
23	99.3	3.6	1.25	0	6.6
24	107.0	3.8	12.0	0	4.2
25	108.7	3.7	0.70	0	3.4
26	108.1	3.5	0.90	0	8.2
27	102.2	4.5	0.94	0	5.1
30	103.0	4.3	0.93	0	4.9
Oct. 1	91.4	4.3	0.90	0	6.8
4	115.7	4.5	1.01	0	39.0
5	108.1	4.6	3.20	0	11.7

Discussion. In a single specimen Winternitz[8] found the chlorid concentration of "white bile" to be 0.761 gm. sodium chlorid per 100 cc. (130 milliequivalents per liter). Elman and Taussig[3] found in 2 specimens a cholesterol concentration of 19 and 45 mg. per 100 cc., respectively, and in 2 others "macroscopic crystals" of cholesterol.

Bernhard[2] and Aronsohn[1] reported that specimens of "white bile" in dog and man which they had examined contained no pigment, bile salt or cholesterol. Bernhard found such fluids to contain approximately 10 mg. per 100 cc. (5 milliequivalents per liter) of calcium. Fowweather and Collinson[4] reported in 6 cases of "white bile" that the calcium concentrations varied from (individual analyses not given) a trace to 15 mg. per 100 cc. (up to 7.5 milliequivalents per liter), and cholesterol values, from a trace to 130 mg. per 100 cc. These data are in general agreement with the more extensive data on "white gall-bladder bile" here reported. The composition of the "white bile" obtained from the gall bladders of the 2 patients from whom it was possible to obtain this over a period of days shows that the single specimen which we obtained was the result of the activity of the mucosal cells lining the gall bladder.

The higher calcium concentrations found in a few of the "white bile" specimens are not so easily explained. Since the cystic duct was occluded, the calcium must have come into the gall bladder with the fluid pouring in from its mucosa. The concentration at which it enters the gall bladder in the usual specimens of "white bile" is approximately at the serum level. The high concentrations found in several of these specimens which were not at all milky suggests that the calcium was present as other than the carbonate salt. Whether under certain circumstances, especially in the presence of infection, it may be secreted in a greater concentration is as yet unknown.

Summary. The "white gall-bladder bile" of the human is similar in its composition to that of the dog. It contains chlorid and, as a rule, calcium at approximately the serum level, the calcium concentrations being slightly more variable than the chlorid variations. The cholesterol concentrations were extremely low, while bile salt was absent.

In one-third of the specimens of "white gall-bladder bile" which we studied the calcium concentrations are considerably above the serum level. The cause of this calcium retention is unknown.

REFERENCES.

1. Aronsohn, H. G.: Pathogenesis of "White Bile," Proc. Soc. Exp. Biol. and Med., **32**, 695, 1935.

2. Bernhard, F.: Experimentelle und klinische Untersuchungen über das Zustandekommen des Hydrops der Gallenwege oder der sog. weissen Galle, Arch. f. klin. Chir., **178**, 495, 1933–1934.

3. Elman, R., and Taussig, J. B.: Cholesterol Content of "White Bile" From Various Sources, Including Contents of "Hydrops" of Gall Bladder, Proc. Soc. Exp. Biol. and Med., **28**, 1070, 1931.
4. Fowweather, F. S., and Collinson, G. A.: Certain Chemical Changes Associated With Gall Stones, With Special Reference to Relation Between Gall Stones and Hypercholesterolemia, Brit. J. Surg., **14**, 583, 1927.
5. Ravdin, I. S., Johnston, C. G., Austin, J. H., and Riegel, C.: Studies of Gall-bladder Function: IV. The Absorption of Chlorid from the Bile-free Gall Bladder, Am. J. Physiol., **99**, 638, 1932.
6. Rous, P., and McMaster, P. D.: Physiological Causes for the Varied Character of Stasis Bile, J. Exp. Med., **34**, 75, 1921.
7. Volkmann, J.: Ueber kalkmilchartige Galle, München. med. Wchnschr., **73**, 2014, 1926.
8. Winternitz, H.: Chemische Untersuchung einer hydropischen Gallenblasenflüssigkeit, Ztschr. f. physiol. Chem., **21**, 386, 1896.

THE DISTRIBUTION AND PROGNOSIS OF PULMONARY LESIONS.*

ASSOCIATED TUBERCULOUS AND NON-TUBERCULOUS.

BY F. MAURICE MCPHEDRAN, M.B. (TOR.)

(From the Henry Phipps Institute of the University of Pennsylvania.)

IN physical diagnosis it has long been recognized that signs in the upper half of the chest are referable to tuberculous lesions, those in the lower half to non-tuberculous.[1] This generalization is applicable, however, only to the adult and that not without exceptions. In early childhood, especially in infancy, it is almost useless, and in adult life chronic tuberculous basal lesions do occur, though rarely.

It is only in the Roentgen ray film, with its capacity for exact definition of anatomical invasion, that it is possible to distinguish in distribution between tuberculous lesions that have been verified by a positive sputum and, on the other hand, chronic non-tuberculous bronchopneumonia,[2] established as such by prolonged observation, showing constantly negative tuberculin reactions and sputum negative for tubercle bacilli. On the basis of these essential differentiating criteria it can be established that there are characteristic sites of origin and spread in the chest for chronic tuberculous and non-tuberculous lesions, from which they depart only in extremely rare instances. Only in the first 6 or 12 months of life do tuberculous lesions originate in, or have their maximum severity in the cardiophrenic angle, the typical site of chronic non-tuberculous bronchopneumonia at all ages. There are also differences in Roentgen ray appearances, especially in later life, even when tuberculous lesions descend into the base.[2,3,4]

* Read before the Association of American Physicians, Atlantic City, May 7, 1935.

In order more briefly and exactly to describe and discuss characteristic differences in site of tuberculous and non-tuberculous lesions, I have divided the lung field into six regions (Plate II, Fig. 2), of which the first three refer to the typical sites of origin of adult-type lesions in the upper third of the lung. The fourth takes in the middle third of the pulmonary cone. It is bounded above by an almost horizontal line and dips in a salient to the diaphragm in the midthoracic line. Within this Area 4 originate the majority of lesions of the childhood type after infancy; of these, the severe consolidations and excavations usually occur in Area 4 mesial, that is, on the posterior chest wall at about the seventh to the ninth rib levels, and the more benign occur chiefly at the anterior second and third interspaces. The lower third of the pulmonary cone contains the last two areas of the lung field, 5 and 6. In this lower third, Area 5 is bound mesially by the heart and mediastinum, below by the mesial half of the diaphragmatic contour, and laterally by an oblique line running from above at the hilum at the posterior level of the eighth or ninth rib, depending on the shape of the chest, to the base of the lung on the diaphragm at the midthoracic line. Essentially this area demarcates the paracardiac border from the anterior to the posterior chest wall, including particularly the cardiophrenic angle. This is the area of acute and chronic non-tuberculous bronchopneumonia; Area 6 is the region into which far-advanced lesions, both tuberculous and non-tuberculous may spread. See Plate II, Fig. 2.

The differentiation of the two lesions has long been an object of investigation;[2,3,4] more recently I have been interested in their relations as they occur in the same chest.[5,6,7] A detailed study has been made and is being continued, based on Roentgen ray observations on clinic patients over some 12 years, with medical histories of the patients and their families.

It has been found that extensive lesions in Area 5, and more particularly severe exacerbations of these non-tuberculous bronchopneumonias, observed in closely spaced serial films, do not intensify tuberculous apical lesions in the same chest, but are, in fact, commonly seen with retrogression of tuberculous lesions. This appears conspicuously in cases that heal with little or no treatment.

A series has been analyzed of 51 cases (Table 1) of tuberculosis under clinic observation that are known to have been sputum-positive and have become sputum-negative without treatment, or with rest short in proportion to the intensity and extent of the disease. These patients were otherwise unselected; the range in age was approximately from 3 to 55 years, only 2 being under the age of puberty; some were negroes. In this, as in other groups, it has appeared that the prognosis for the tuberculous lesion has been more favorable when it has been associated with a relatively extensive Area 5 lesion. On the other hand, it has appeared that the younger the patient, the greater his danger if the associated lesion

in Area 5 tends to heal. Indeed, relapse of tuberculosis in many cases has followed the healing of a lesion in Area 5, during the acute stage of which the apical lesion had retrogressed. In those whose sputum had become negative, but whose tuberculous lesion still appeared unstable, only relatively small cardiophrenic lesions were seen. In those patients whose sputum, once positive, had been negative for many years when first seen, extensive or residual lesions were usually found in Area 5.

TABLE 1.—SUMMARY OF ALL CASES OF SPUTUM+ TUBERCULOSIS BECOMING SPUTUM− WITHOUT THERAPEUTIC PNEUMOTHORAX AND WITH LITTLE OR NO OTHER TREATMENT: OBSERVATION 1923 TO 1935.

Total number of cases	51
Age at first sputum + examination:	
Under 10 years	2
10 to 45 years	40
Over 45 years	9
Average number of years sputum − since last sputum +	8
Tuberculous lesion:	
Minimal	13
Moderately advanced	24
Far advanced	14
Cardiophrenic lesion:	
Severe	31
Marked	15
Slight	3

Age. When the sputum was first positive 40 of the 51 cases were between the approximate age of puberty and 45 years; only 2 were under 10 years; 8 were between 45 and 55, and 1 was 78. Of the far advanced cases, 10 were under 30 years.

Negative Sputums. Only 2 cases were listed as sputum negative when less than 2 years had elapsed since the last positive sputum. One of these is illustrated in Fig. 2.

Classification of Lesions. Of the 13 minimal cases, all had become sputum negative before Roentgen ray examination was made. It is probable that the lesions had retrogressed materially by the time these cases came under observation; 12 lesions had the linear appearance of old scars.

Of the 24 moderately advanced cases, 7 would be transferred to the far advanced group if all of the pulmonary damage were considered tuberculous. In the table, only that part of the involved area that is regarded as clearly tuberculous (upper two-thirds) has been made the basis of the grouping. Several of the minimal cases would similarly fall under moderately advanced according to standard classification.

As with the minimal lesions, some of the moderately advanced group were observed after the sputum had become negative, and therefore presumably after their tuberculous lesions had retrogressed somewhat.

Deaths. Of the 51 cases 5 are dead, all of causes other than tuberculosis. One died, aged 39, of a pituitary tumor. His sputum was consistently negative in 21 examinations for 5 years before death. Roentgen ray examination 1 month before death showed slight apical scars and a moderate basal lesion. Autopsy showed a scarred and calcified tuberculous lesion and a residual chronic non-tuberculous bronchopneumonia, which had been subject to marked exacerbations during the 5 years preceding death. One child had extrapulmonary (bone) tuberculosis.

One died, aged 42, of a "heart attack" 14 years after his sputum had ceased to be positive. When last examined, 7 months before death, the tuberculous lesion was minimal, the basal lesion severe. The sputum was negative 37 times, including 2 animal inoculations, in the 4 years preceding death. One child has moderately advanced, and one far advanced tuberculosis.

One patient died, aged 62, of apoplexy. He had been well and was looking for work when the stroke occurred. Sputum was negative for 3 years and absent for 1 year before death. His wife and 2 children had died of tuberculosis.

One died in his 64th year, 16½ years after the sputum had last been positive. The apical lesion was minimal and scar-like 7 months before death, while the basal lesion was severe.

One patient died, aged 82, of perforated gastric ulcer, 4 years after the sputum had last been positive, as determined by smear and animal inoculation. Postmortem examination showed a densely scarred apex typical of old tuberculosis, and an extensive chronic non-tuberculous pneumonitis of the middle and lower lobes with secondary moderate bronchiectasis. At least 1 child died of tuberculosis.

Lesions may be found in Area 5 in association with progressive tuberculosis, but they have been slight in extent or fleeting, or they have appeared after the tuberculous lesion was far advanced and well entrenched.

In infancy a non-tuberculous lesion may have a remote adverse influence upon tuberculous infection, even in the absence of an extensive or definite tuberculous lesion in the lung parenchyma.[5,6] The effect, however, is apparently a purely mechanical one, the increased lymph drainage flooding nodes that were demonstrably grossly enlarged and, therefore, presumably the site of many young tubercles.[2] This flooding is most common as a result of bronchopneumonia, whether associated with measles or not. Aside from these cases, the occurrence of a non-tuberculous bronchopneumonia is associated in very young children, just as in older patients, with retrogression of tuberculous pulmonary infiltration. No evidence has been found that a non-tuberculous bronchopneumonia (Area 5 lesion) has aggravated an associated tuberculous pulmonary lesion at any age, and in the spontaneous retrogression of tuberculosis, a non-tuberculous element has commonly been a part.

It is evident that the method of examination is of the first importance in the study of such an interrelationship, which can be observed only in suitable roentgenographic views of the living. In the present study stereoscopic films have been synchronized to minimize the effects of cardiovascular movement, the importance of which has been discussed elsewhere.[3] In the base of the lung, particularly, slight infiltrations may be overlooked or shadows may be mistaken for lesions in the blurring of trunk markings and of the cardiac border.[2] Hardly less essential to exact demonstration of slight lesions among the complex shadows beside the heart on the right, and on the left behind the cardiac contour, are multangular views. The patient is rotated so that the incident beam of the

Roentgen ray forms an angle of 5, 10, 15, 20, 30, 45 or 60 degrees with the sagittal plane of the body, the degree of rotation depending on the area to be thrown clear of the cardiac silhouette. Only in this way can consolidations in this region be exactly defined. Due regard is had to adapting the quality of the film so that it best records the critical density of a small lesion against a varied background of heart and vessels. The high-speed Bucky diaphragm[9] may be used for observations of particularly obscure areas.

Moreover films must be closely spaced to catch the opposed rhythm that has been repeatedly observed in these studies, of apical retrogression with or shortly after basal spread, and of apical spread following basal retrogression. The retrogression of the apical lesion may not become obvious until after the paracardiac lesion has reached its peak, which may be a matter of 4 to 8 weeks. In retrogressive tuberculosis the Area 5 lesion characteristically persists while the tuberculous is decreasing, as suitably spaced films will show. There is, however, in many typical cases with favorable outcome a stage at which the paracardiac has become much less conspicuous while the apical continues to show marked retrogression. Films taken according to the rise and fall of symptoms may be made when the paracardiac infiltration is reaching its peak and then not again until both the apical and the Area 5 lesions have retrogressed materially. Such views would show only a coincident increase and decrease of both, and by themselves entirely misplace the emphasis and misinterpret the interrelationship of the two lesions.

Of the cases that have been observed for years by this method, a large series has recently been reviewed and will be presented shortly.* A few typical cases are described here and are illustrated by diagrams traced from the films.

Cases of Uncomplicated Non-tuberculous Pulmonary Lesions. In Plate I, first row, are shown diagrammatically typical uncomplicated non-tuberculous lesions in 4 members of a white family with consistently negative sputums, a conspicuously high incidence of negative tuberculin reactions, and no known contact with tuberculosis. The father, aged 41 years and 2 months, on April 29, 1927 (Fig. 1), had occasional "colds," with some cough and expectoration. In March, 1929, he had a severe attack, with fever and weakness; the sputum, scanty, blood-streaked, was negative for tubercle bacilli. Sinusitis.

A daughter, aged 16 years and 2 months, on May 6, 1933 (Fig. 2), had for years suffered from attacks of cough. Sputum was negative on animal inoculation. Serial Roentgen ray examinations showed a fluctuating density obscuring the left cardiac border. Basal râles were heard in 1932 and 1933. With the exception of her parents, she was the only member of the family to have consistently positive tuberculin reactions from the time of her first examination, at the age of 8 years and 10 months.

In the third eldest child, a boy, aged 5 years and 1 month, on June 7, 1925 (Fig. 3), a non-tuberculous basal lesion was observed from 1925 through 1933; during this time his tuberculin reaction was consistently negative

* Exhibit, National Tuberculosis Association, June, 1935, and subsequent publication.

FIGS. 1, 2, 3, 4.—Non-tuberculous lesions in four members of a white family. See text.

FIGS. 5, 6, 7, 8.—Non-tuberculous basal lesions and lung abscess in young white adult. See text.

FIGS. 9, 10, 11, 12.—Progressive uncomplicated tuberculosis in young white adult. See text.

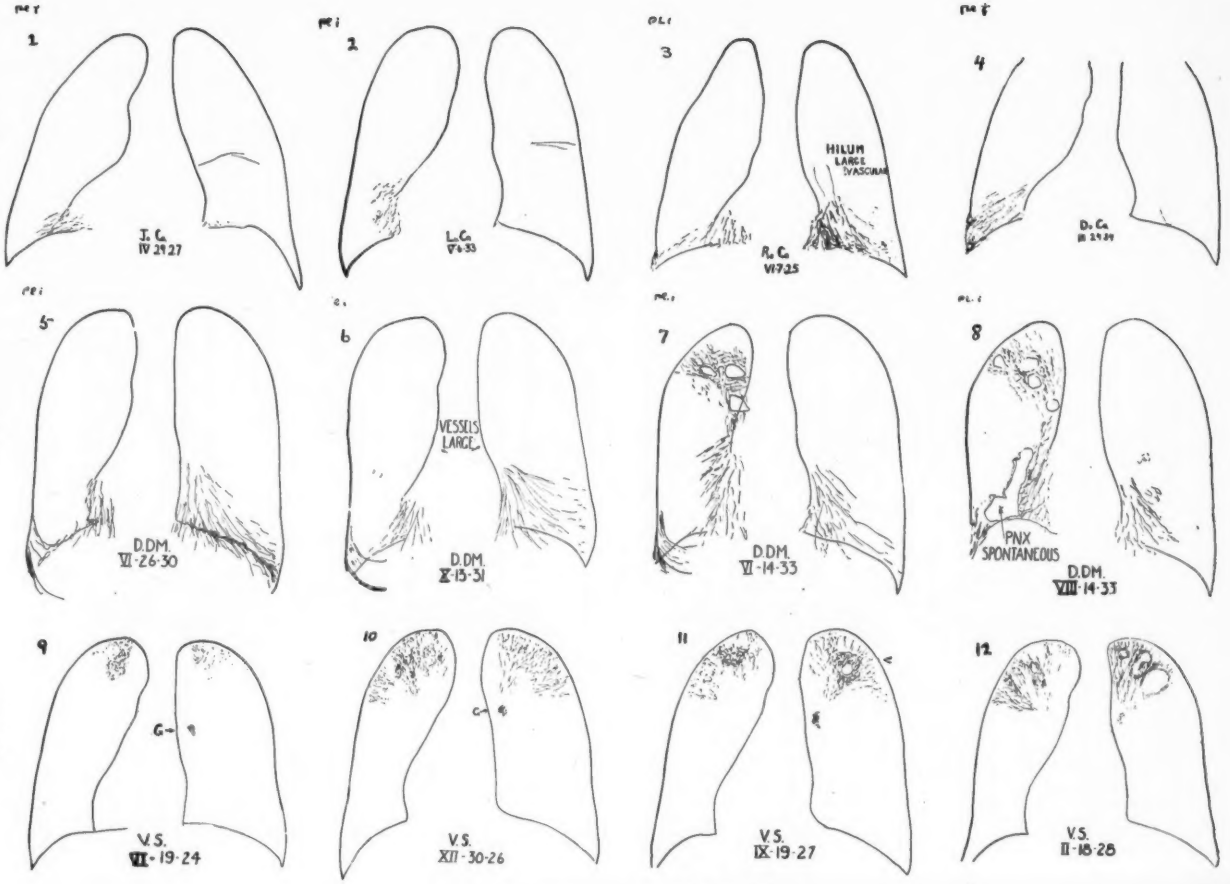


PLATE I.—Diagrams traced from films.

to 1 mg. O.T. until he was inoculated, in 1932, with killed tubercle bacilli, in a study carried on by a department of the Institute, when it became ++ to 1 mg. O.T. His sputum was negative for tubercle bacilli 8 times from 1926 to 1931 in smears and twice on animal inoculation. No spirochetes or molds. Gram-negative and Gram-positive diplococci and influenza bacilli reported on culture.

Clearing of infiltration was noted in films of February, 1927, as compared with those of 1925; subsequently wide fluctuations were seen in serial films. Many râles were heard in numerous examinations over the bases and sometimes throughout the lung. Cough was present with exacerbations from 1925, except for intervals of varying duration; expectoration was usually moderate, sometimes greenish. There was no history of other illness except pertussis in 1926.

The youngest child, aged 7 years and 7 months, on March 24, 1934 (Fig. 4), was first seen at 8 months. He has a history apparently dating from 1928 of acute attacks of coryza, cough, usually unproductive, sometimes with fever, sometimes with gastric symptoms; in good condition between attacks. Expectoration, greenish, was first reported in May, 1934. Roentgen ray, May 14, 1932, showed light spots at the base near the heart, right and left, which were interpreted as old bilateral basal lesions, probably non-tuberculous. The film illustrated in the diagram showed, on the right, prominent bronchi and a few strands in the lower third, and, on the left, a confluent patch, almost homogeneous, in the outer two-thirds of the area above the diaphragm (Area 6). Râles were heard in May, 1934, and again in May, 1935. The tuberculin reaction was negative to 1 mg. O.T. until it became ++ to 1 mg. O.T. in 1931 and again in 1932; it was negative to 0.005 mg. P.P.D. in 1934 (age, 8 years).

It is noteworthy that in this family of 6 children the tuberculin reactions were consistently negative for 37 person-years and fluctuated for 7 person-years. Positive sputum was never obtained from any member of the family. Elsewhere[4] attention has been drawn to the family incidence of these lesions.

The second row of Plate I shows, in a white boy, aged 15 years and 8 months, on June 26, 1930 (Fig. 5), the development of an Area 5 lesion, with bronchiectasis, subsequent involvement of the upper two-thirds of the lung (pulmonary abscess) and death with brain abscess, November 4, 1933. Sputum was negative for tubercle bacilli 27 times from 1925 to 1933, as were also the bronchoscopic findings shortly before death. Tuberculin reaction positive to 1 mg. O.T., November 7, 1927; negative to 1 mg. O.T., January 23, 1929, August 1, 1930, and September 14, 1931.

History of pneumonia at 2½, 9 and 13 years. No known contact with tuberculosis. Hemoptysis, 1925; sputum occasionally blood-streaked. First seen in 1925 with occasional cough, expectoration and headaches. Cough, especially at night and mornings, from 1927, with "slight to moderate" greenish expectoration.

In June, 1930, the patient was 20 pounds underweight. In 1932, cough and expectoration were improved, with gains in weight, after treatment by postural drainage. A few râles were heard at the bases in two examinations, 1932 and 1933.

In June, 1933, after a long trip and exposure to rain, he had an acute illness, with high fever, pleurisy in left side, a loss of 15 pounds in 1 week, considerable cough and expectoration. Weakness and cough continued, with about 8 ounces of sputum daily. Roentgen ray showed consolidation in Area 5, right and left, and in addition, on the left, confluent spots in the middle third, and consolidation with excavation in the upper third. Two sputum examinations were negative. The patient was hospitalized, with a diagnosis of confluent bronchopneumonia, probable bronchiectasis and

PLATE I.—Diagrams traced from films.

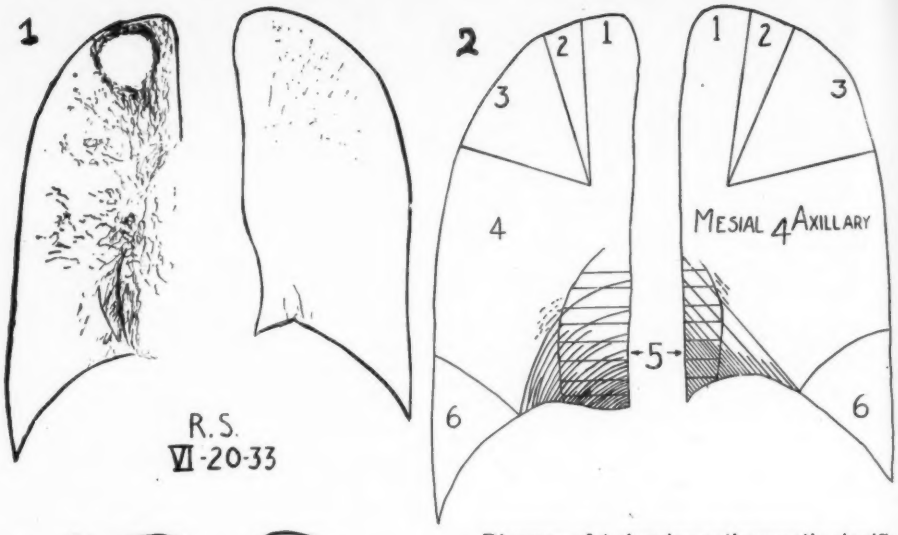
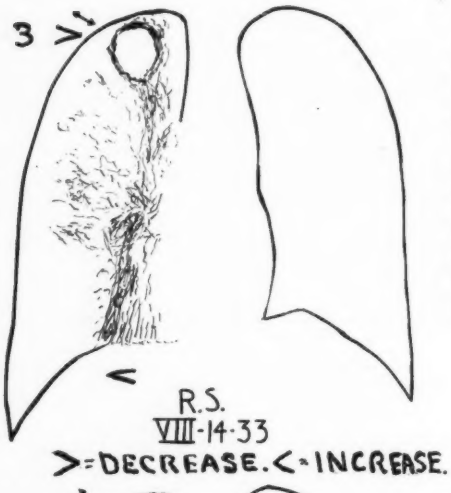


Diagram of 1 showing pathogenetic significance of several lung areas. Nos. 1, 2 and 3 are typical sites of adult tuberculosis. In No. 4 originate from the third to eleventh year characteristic tuberculous lesions, those postero-mesial often with cavity, those antero-axillary usually benign. No. 6 is an area of spread. No. 5 is the area of nontuberculous bronchopneumonia and of mixed tuberculous and nontuberculous lesions, both associated with apical healing. Intensity of shading corresponds to significance of distribution of persisting lesion.



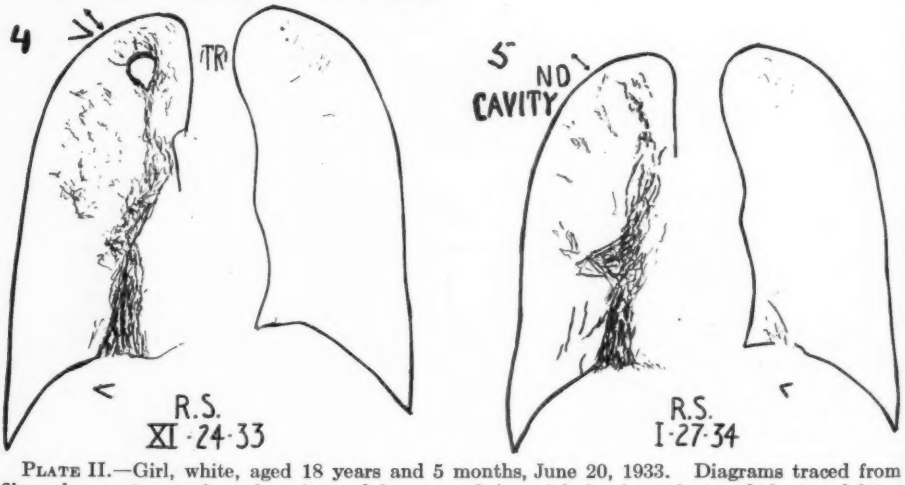


PLATE II.—Girl, white, aged 18 years and 5 months, June 20, 1933. Diagrams traced from films show retrogression of cavity and increase of Area 5 lesion in patient ambulant and later working. Sputum formerly positive became negative.

lung abscess. Bronchoscopy, July 3, 1933, by Dr. L. H. Clerf, found a large quantity of pus coming from the orifice of the left upper lobe bronchus, the mucosa of which was intensely inflamed. Culture of the pus showed chiefly B. influenzæ and a few Micrococci catarrhalis; it was negative for acid-fast bacilli and spirochetes. Other sputum cultures (not bronchoscopic) showed Strep. viridans, B. influenzæ and M. catarrhalis in three specimens; 7 sputum examinations were negative for acid-fast bacilli. There was no cardiac enlargement or displacement; no murmurs.

On November 1, 1933, the patient was again admitted to the hospital, unconscious, with a diagnosis of brain abscess or meningitis. He died, November 4, 1933. Postmortem examination showed partial healing of lung abscesses at apex of left lower lobe and dense fibrous scarring of both bases, with moderate cylindrical bronchiectasis traversing the scarred areas.

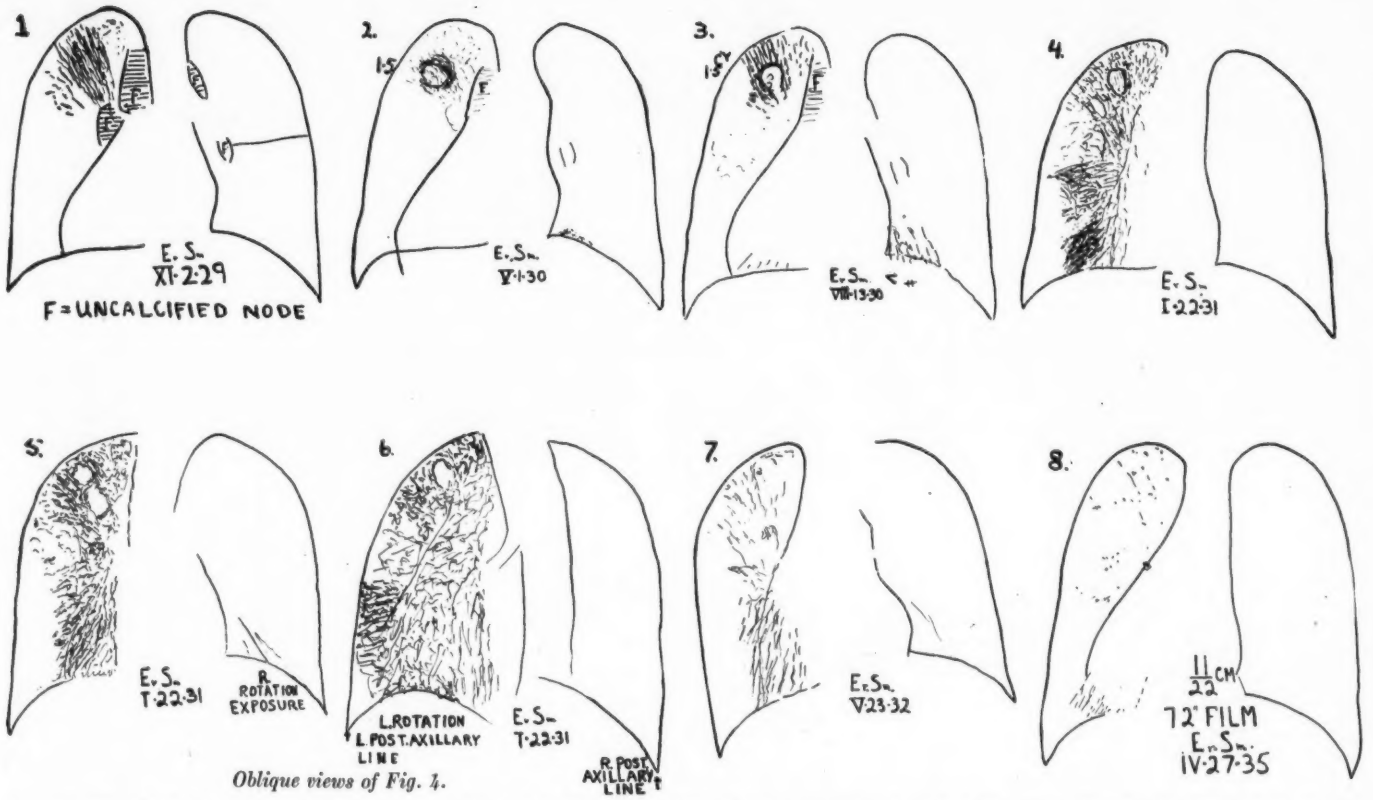
A Case of Progressive Uncomplicated Tuberculosis of Adult Type. In the last row of Plate I are shown diagrams from films of a boy, white, born March 27, 1912. These show uninterrupted progression of a tuberculous lesion with no lesion in Area 5 (see Figs. 30, 31 and 32 of Ref. 2). This boy's father died of pulmonary tuberculosis; his brother had a tracheobronchial calcification. Serial films showed that his lesions originated in and descended from the extreme apex. In June, 1924 (Plate I, Fig. 9), there was "soft" mottling down to the fourth posterior interspace, right and left, and a calcified hilum lymph node at the eighth rib, right. The tuberculin reaction was +++ to 0.01 mg. O.T. The weight was 106%. There were no symptoms and only transitory signs; a few râles were heard at one examination only.

The boy did not receive rest adequate to the increasing Roentgen ray density, probably because he looked very well, had good color and remained above normal weight, with steady growth and splendid physique. By March, 1928, sputum had become positive and the lesion far advanced, with consolidation and excavation. To continue with the serial review of the case:

On December 30, 1926 (Plate I, Fig. 10), the infiltration on the right above the clavicle was denser and there was a patch at the fifth rib at the axillary line posteriorly, and a calcified node at the seventh posterior rib and interspace. On the left there was moderately dense infiltration above the posterior fifth rib. Physical signs reported absent. The tuberculin reaction was ++ to 0.01 mg. O.T., the temperature normal and the weight 103%. Animal inoculations of throat swabs and feces were both negative. The general condition of the patient was apparently excellent, and the report of spread seen roentgenographically was not used to guide the treatment.

The patient was in a hospital, but ambulant, from August, 1926, to August, 1927. He was discharged as well enough for school, still having no symptoms and only trivial signs, but with Roentgen ray evidence of increased density in both apices with a small cavity on the right. Against our advice he went to school until February, 1928, when he came to the dispensary with slight cough of 2 weeks' duration. His sputum was positive. Impairment was heard over both apices, with a few fine râles over the right. He said he felt well; his weight was 101%.

In this case there is shown typical progression of an uncomplicated tuberculous infiltration to far-advanced extent. There was no infiltration in Area 5 until the tuberculous lesion was even farther entrenched than it appears in Fig. 12 (Plate I). In September, 1928, a small density occurred in the upper part of Area 5. It was trivial in relation to the extensive damage of both lungs, each of which showed sufficient tuberculous invasion to warrant a classification of far-advanced tuberculosis. The boy died, October 31, 1929.



Oblique views of Fig. 4.

PLATE III.—Girl, colored, aged 10 years. Lesion in left apex fluctuating after appearance of small right paracardiac density (Figs. 1, 2, 3) and clearing after marked extension into Area 5 (Figs. 4, 5, 6). Fig. 7 shows marked retrogression of tuberculous lesion in left apex with persistence of "soft" basal density. Fig. 8 shows healed tuberculous lesion, persisting "soft" Area 5 lesion. Diagrams traced from films.

Two Cases of Associated Tuberculous and Non-tuberculous Pulmonary Lesions. Plate II illustrates diagrammatically these associated lesions in a girl, white, aged 18 years and 5 months, on June 20, 1933 (Fig. 1), when Roentgen ray examination showed, on the right, a few medium-sized ill-demarcated spots in the upper third, a few linear spots in the cardiophrenic angle (Area 5). On the left, at the posterior third and fourth interspaces there was a cavity, 3.5 cm. in size, surrounded by dense infiltration that descended as scattered and grouped large and medium-sized dense flocculent spots through the upper three-quarters of the lung field, chiefly mesial; in the lower quarter left there were linear spots upon the cardiac border. By August 14, 1933, after 6 weeks' hospitalization, the cavity had decreased in diameter, receding from the axilla mesially in a somewhat eccentric contraction, as is seen commonly with apical cavities associated with Area 5 infiltrations. The infiltration elsewhere in the upper three-quarters had decreased, that in the lower quarter had increased definitely, so that it now completely obscured the left cardiac border and spread out upon the diaphragm, causing a marked broadening in the apparent width of the heart shadow, especially where this passed over into the silhouette of the diaphragm. Instead of the acute cardiophrenic angle of June, there was a definitely obtuse angle, and the cardiac silhouette could be faintly perceived through the dense confluent linear spots that obscured the left border of the heart.

The patient continued ambulant and toward the end of the year began to work. The cavity had retrogressed further by November, continuing its eccentric contraction toward its mesial wall, and the infiltration elsewhere had likewise retrogressed, except that in Area 5 upon the cardiac silhouette and the adjacent diaphragm, which continued to increase slightly but definitely. This density upon the heart persisted into March, 1935, while the infiltration in the upper three-quarters continued to recede. In the last observation there were only a few dense spots in the upper three-quarters of the lung field. These were scattered except mesially, where they formed a light network.

Noteworthy in this case is the uninterrupted retrogression of the cavity after the patient got out of bed, at a rate not less while she was ambulant than when she was at rest. The only other consideration in the history is a tonsillectomy under local anesthesia in October, 1933. The films of June, August, November, 1933, and January, 1934, indicate that the operation had no relation to the rate of retrogression of the cavity and associated tuberculous infiltration.

Plate III shows diagrams of a girl, colored, aged 10 years, on November 2, 1929 (Fig. 1). At this time there was almost homogeneous infiltration in the left upper third and enlargement of associated nodes. In March, 1930, a small infiltration appeared on the right in Area 5. There was slight retrogression of the left upper third consolidation, but a cavity, 1.6 cm. in diameter, could now be perceived at the posterior fifth rib and interspace. The infiltration right and left fluctuated in extent until January, 1931, when there was a marked increase of infiltration throughout the left lung, extending to the diaphragm and wholly obscuring the left cardiac silhouette in the posteroanterior, and in both the right and left oblique views (Plate III, Figs. 4, 5 and 6). The patient had some rest at home and was hospitalized for 10 months, to January, 1932, with no additional rest. By March and May, 1932, reëxamination showed a marked recession of the infiltration throughout. The apical tuberculous lesion was represented by a few scattered linear spots, but there were persisting grouped spots upon, behind and lateral to the cardiac silhouette, that is, in Area 5. The heart was now markedly enlarged. The electrocardiogram showed a left axis deviation, and there were physical signs of mitral insufficiency. By

April, 1935, the cardiac shadow had diminished slightly but was still definitely enlarged. In May, 1935, the patient returned with a recurrence of infiltration surrounding the cardiac apex (Area 5), a relapse of her nontuberculous bronchopneumonia. The left apical tuberculous lesion was represented only by calcified spots and a few dense strands. It was apparently healed, in association with an unstable fluctuating or recurrent nontuberculous bronchopneumonia.

Discussion. It is obvious that the conception of mutually opposed activity illustrated in the case histories shown in diagrams in Plates II and III, could not be based upon a few cases only, however striking they might be, but, as intimated above, has grown from detailed study for many years of a large series of cases. The 2 patients chosen for illustration are young women, one of them colored; age, race, sex, inadequacy of treatment were all unfavorable for the arrest of tuberculosis. Similar observations have been repeatedly made in patients of all ages, both sexes, white and negro, when serial films have been spaced closely enough to obtain exact information as to the distribution and intensity of lesions throughout the lung. These cases will be reported in detail as rapidly as possible.

A disadvantage of tuberculosis work, that it is not always possible to carry out adequate treatment, may be an advantage to the clinical investigator who takes the opportunity to follow the results of various treatments, and to observe the natural evolution of the disease. When there is a marked lesion in Area 5 it has been not uncommon to find patients suffering from malaise, cough, expectoration, in short the classical evidences of pulmonary tuberculosis, gradually show an improvement in strength and a decrease in symptoms while continuing ambulant and at work. The clinical improvement is accompanied by a retrogression of the apical density and a contraction of its cavities, while the basal density diminishes slightly, persists unchanged, or may even increase. Retrogression of the apical density may be extremely rapid, and uninterrupted or fluctuating concentric diminution of cavities may be seen in serial films occurring within a matter of weeks.* In brief, when there is a severe lesion in Area 5 an extensive and excavated apical lesion with positive sputum may retrogress to scarring and negative sputum in an ambulant patient in a manner excelling what would be expected with artificial pneumothorax or absolute rest in bed.

In closely spaced serial films made from many angles it has been frequently observed that increase of a basal lesion is shortly followed by diminution of the apical density with contraction of its cavities. In some cases of tuberculosis of short duration, a marked increase in an Area 5 lesion has been followed by complete scarring of an extensive, excavated tuberculous lesion. In cases of relapsing

* Healing in tuberculosis may occur uniformly throughout the lungs, and this appears to be the rule when there is a lesion in Area 5. In other cases that recover, healing is usually irregular, often with retrogression in one patch and simultaneous increase in another, perhaps closely adjacent area of the lung.

tuberculosis, on the other hand, retrogression of an associated Area 5 lesion has been observed until it is represented only by a few sharp strands, or fine unclouded diaphragmatic peaks. Following the basal retrogression the apical lesion increases. In the absence of adequate treatment, the future course of the lesion has appeared to have a relation to subsequent exacerbation of the lesion in Area 5, and to the extent, severity and permanence of this exacerbation. After the arrest of an apical lesion, cough and expectoration, consistently negative for tubercle bacilli, may persist for many years, and may cause disability as severe as the tuberculosis. As pointed out elsewhere, such cases are often mistakenly diagnosed "benign tuberculosis of middle age."[7, 10, 11, 12]

Many factors play a part in the ebb and flow of the processes involved in tuberculosis. It is axiomatic, and a justification for research, that we have only an imperfect knowledge of the balance of factors that occurs when tuberculosis is arrested in the natural course of the disease or, indeed, when aided by rest. It is evident that the observations reported here could not be made by the methods of pathology, bacteriology, or other laboratory study, or by the usual clinical examination, but only by a method permitting exact exploration of the chests of the living. The criteria of roentgenographic examination, described fully elsewhere,[2] are based on earlier studies of excised lungs.[8, 13] The writer's interpretation of the observations is that the lesions in the cardiophrenic angle are non-tuberculous, in whole or in part, that their exacerbations are characteristically accompanied or followed by retrogression of associated tuberculous lesions elsewhere in the lung field, and that in the series of cases studied this interrelationship has been a significant factor in "the natural tendency of the disease to retrogress." It is obviously impossible to measure or define exactly all the factors that may be concerned. It has long been well established that under experimental conditions a relative resistance against reinfection may be conferred by a previous infection with tubercle bacilli, but in general our conceptions of all that is implied in tuberculosis by the terms immunity, allergy, sensitization, are incomplete and confused, especially as applied to the complexity of natural conditions. The observations described above cannot be readily explained in the terms of immunology, but they appear to have a bearing on the wide problem of the resistance of the host to tuberculosis. It is hoped that other studies now in progress will throw further light on this phenomenon.

Summary. In serial Roentgen ray films it has been found that even in children, in whom tuberculous lesions characteristically do not originate in the upper third of the lung field, there is a sharp difference in distribution of the lesion between tuberculosis, on the one hand, and chronic non-tuberculous bronchopneumonia and bronchiectasis, on the other. Tuberculous lesions of childhood typically are situated in the middle third; those that are severe

and excavated are usually based on the posterior chest wall, the slighter ones on the anterior chest wall. Chronic non-tuberculous bronchopneumonia at all ages almost invariably originates and has its maximum severity in the cardiophrenic angle, whence during exacerbations it spreads along the diaphragmatic contour. Such lesions are associated with persistently negative sputum and, in children, with tuberculin reactions consistently negative for years.

In a comprehensive series of cases, sputum-positive lesions, of both childhood and adult types, that have become sputum-negative with little or no treatment have been observed in closely spaced multangular views. In such cases, tuberculous lesions in association with active and persistent cardiophrenic lesions have retrogressed rapidly, with contraction of cavities and disappearance of tubercle bacilli from the sputum. With complete arrest of the tuberculous lesion, the cardiophrenic lesion may fluctuate for years, with persistently negative sputum. On the other hand, in many clinic cases relapse of tuberculosis has followed healing of a lesion in the cardiophrenic angle, during the acute stage of which the apical or childhood type lesion had retrogressed. Lesions that according to the accepted classification are far advanced because the greater part of the lung is involved, including the cardiophrenic angle, have had a more favorable course than lesions of lesser extent and severity confined to the upper two-thirds of the lung fields, or invading the cardiophrenic angle only in terminal stages.

Acknowledgment is made to Miss Eleanor S. Cooper for assistance in the preparation of this paper.

REFERENCES.

1. Riesman, D.: Chronic Nontuberculous Bronchopneumonia, J. Am. Med. Assn., **102**, 673, 1934. Norris, G. M., and Landis, H. R. M.: Diseases of the Chest, 5th ed., Philadelphia, W. B. Saunders Company, 1933.

2. McPhedran, F. M.: The Diagnosis and Classification of Pulmonary Tuberculosis in Childhood and Adolescence, Am. Rev. Tuberc., **20**, 532, 1929.

3. McPhedran, F. M.: The X-ray Diagnosis of Pulmonary Tuberculosis in Children, Ibid., **16**, 420, 1927.

4. McPhedran, F. M.: Chronic Infectious Nontuberculous Lesions of Childhood and Their Relation to Bronchiectasis, J. Clin. Invest., **7**, 512, 1929.

5. McPhedran, F. M.: Tuberculous and Nontuberculous Pulmonary Infections in Infancy and Childhood, Penna. Med. J., **37**, 985, 1933–1934.

6. McPhedran, F. M.: Observations on Associated Tuberculous and Nontuberculous Pulmonary Lesions, J. Clin. Invest., **14**, 718, 1935.

7. McPhedran, F. M.: Coincident Tuberculous and Nontuberculous Pulmonary Infiltrations: A Group of Cases, Am. J. Roentgenol. (to be published).

8. McPhedran, F. M., and Weyl, C. N.: Automatic Synchronization of Roentgen Ray Exposures, Am. J. Med. Sci., **169**, 510, 1925; Clinical and Physiologic Deductions from Synchronized Roentgen Ray Exposures, Ibid., **173**, 313, 1927.

9. Wilsey, R. B.: Scattered Radiation in Roentgenography of the Chest, Preliminary Report, Radiology, **23**, 198, 1934.

10. McPhedran, F. M.: The Roentgenogram in Early Tuberculosis in Adults, U. S. Naval Med. Bull., **30**, 91, 1932.

11. Fishberg, M.: Infraclavicular Tuberculous Infiltrations, Am. Rev. Tuberc., **17**, 1, 1928.

12. Douglas, B. H., Pinner, M., and Wolepor, B.: Acute Subapical Versus Insidious Apical Tuberculosis, Preliminary Report, Ibid., **19**, 153, 1929.

13. McPhedran, F. M.: The Diagnosis of Tracheobronchial Tuberculosis, Am. J. Med. Sci., **173**, 245, 1927.

ELECTROCARDIOGRAPHIC CHANGES DURING ENCEPHALOGRAPHY (20 CASES).

By Milton M. Abeles, M.D.,
RESIDENT NEUROLOGIST, MONTEFIORE HOSPITAL,
AND
Daniel E. Schneider, M.D.,
RESIDENT NEUROLOGIST, MOUNT SINAI HOSPITAL, NEW YORK CITY.

(From the Neurologic Services of Dr. S. P. Goodhart of Montefiore Hospital and Dr. I. Strauss of the Mount Sinai Hospital.)

Clinically, pulse changes and other signs of vagus effects such as vomiting, pallor, sweating and variations in blood pressure have often been noted, during the injection of air in encephalography. In addition, there may be usually a slight rise in temperature, meningeal signs, headache and, during the passage of air upward, pain along the nerve roots.

The pulse changes have been described by various authors. In a typical description by Krause,[1] he points out that the pulse becomes slower, arrhythmic, small and weak and that pulse as well as accompanying respiratory changes for the most part soon disappear. Fay[2] states that the slowing of the pulse to 60 beats per minute is not uncommon. A number of observers have reported an initial acceleration of the pulse rate. Juzelevsky[3] describes a case in which the patient's pulse could not be felt and the patient appeared to be on the verge of collapse. In almost every case of encephalography, however, there are minor signs of shock probably due to vagus stimulation.

Since we were unable to find in the literature any but clinical observations of the pulse changes, it seemed probable that simultaneous electrocardiography would yield further valuable information.

Technique. The patients were prepared by omitting lunch and giving a hypodermic injection of Magendie's Solution m. vii and Hyoscine gr. 1/150, from $\frac{1}{2}$ to $\frac{3}{4}$ hour before beginning the procedure. The patients were all in the sitting position in the encephalographic chair. Entry into the subarachnoid space was made *via* the lumbar route. At the same time the limbs were prepared for electrocardiography and a control electrocardiogram taken. In 3 cases, a record was taken every 10 minutes from the outset, at the first injection of air. In the remaining cases, tracings were obtained during the period when the pulse began to decrease in rate, and at intervals when the changes in pulse indicated that the more accurate record was necessary. The technical facilities at our disposal were such that continuous records were not feasible. Blood pressure was observed but not correlated with simultaneous electrocardiograms. Our readings, however, tended to confirm the already established facts, that the blood pressure rises during the injection of air and then gradually falls to normal within 8 to 36 hours.[4] Pulse rates were noted in each case at 15-minute to 30-minute intervals for as long as the pulse remained below 60 *after* the injection of air was discontinued. This, of course, varied with the individual case.

TABLE 1.—ELECTROCARDIOGRAPHIC CHANGES DURING ENCEPHALOGRAPHY.

No.	Age.	Electrocardiographic changes.	Positive encephalographic findings.	Blood pressure.	Spinal fluid pressure (water).	Fluid/Air ratio.	Diagnosis.
1	19	Marked S. A. Occa. V. E. S. L. V. P. *P*2 and *P* 3 inverted. Suggests interference with nervous mechanism	Cortical atrophy (left parietal).	100/90	110 mm.	125/95	Idiopathic or post-traumatic epilepsy.
2	12	S. A. In records Nos. 2 and 3 the *Q*-*R*-*S* waves are of lower voltage than in record No. 1 before encephalography	Normal	120/80	Low	102/82	Idiopathic epilepsy.
3	49	Migration of the pacemaker in Lead 3	Air in subtentorium. Cortical markings on both sides exaggerated	112/86	120	190/145	Idiopathic or post-traumatic epilepsy.
4	46	No appreciable change during injection of air. R_3 low	Normal	140/90	90	185/145	Idiopathic epilepsy.
5	20	Slight S. A. accentuated during encephalography with the production of bradycardia	Cortical atrophy (right parietes (?))	115/70	70	145/110	Idiopathic epilepsy.
6	8	Considerable S. A.	Sl. enlargement of 3d and 4th ventricles. Basal cistern dilated	110/80	Low	90/70	Idiopathic epilepsy.
7	13	First record: S. T. rate 165/min. The second record showed periods of phasic sinus slowing with an *A*-*V* nodal rhythm	No air in vent. system. Cortical markings good	100/80	60	120/115	Diffuse degen. Cerebral disease. (Congenital).
8	8	S. A.	Hugely dilated vent. system—symmetrical	124/80	150	.....	Degenerative disease marked int. hydrocephalus.
9	41	Migration of cardiac pacemaker between the *S*-*A* and *A*-*V* nodes. Periods of S. A. with transitory nodal rhythm	Normal	110/60	100	.....	Post-traumatic encephalopathy.
10	40	Rate 48/min. 2 hours after encephalography	Subarachnoid markings exaggerated and basal cistern enlarged	140/80	Low	200/165	Traumatic encephalopathy.
11	54	Sinus bradycardia, rate 48/min. *R* and *T* lower in second record than in first	Moderate dilatation of vent. Much air in subarachnoid space	150/90	Low	260/210	Traumatic encephalopathy. Lues?
12	55	Low voltage in all leads. L. V. P.	Mod. dilatation of the vent. system. Much air in subarachnoid spaces.	140/80	Low	330/245	Alzheimer's disease.
13	34	Bradycardia of 50–60/min. Main deflection shows widening. Notching in all leads. T_3 inverted. *R*-*T* transition slightly abnormal in Leads 1 and 3	Slight asymmetry of lat. vent., left larger than right 3d vent. normal	112/76	100	150/125	Traumatic encephalopathy.
14	28	S. T., rate about 135/min. In Leads 2 and 3 rate slower with periods of sinus slowing, too far apart to be regarded as respiratory. Probably a form of sinus depression	Unusual collection of air in subtentorium bilaterally. Otherwise normal	.....	160	145/115	Traumatic encephalopathy? Hysteria?
15	41	Marked bradycardia, 60/min. Shallow *T* in all leads	Slight depression of left lateral vent. Air over left cortex	188/133	230	98/83	Oxycephaly. Pituitary tumor.
16	42	Left vent. preponderance	Vent. not outlined. Much air in subarachnoid space	120/90	110	.....	Left frontotemporal. Neoplasm.
17	45	Sinus tachycardia, 100/min.	Intervent. septum displaced to right; left vent. displaced downward. Cortical markings absent on left. Much subtentorial air bilaterally	130/90	120	105/90	Left temporal neoplasm.
18	3½	S. A.	Symmetrical and enormous dilatation of entire vent. system	.....	60	250/220	Congenital communicating hydrocephalus.
19	56	No change	Symmetrical dilatation of the vent. system and much air in subarachnoid spaces	200/110	160	200/180	Cerebral arteriosclerosis.
20	35	A. F. and nodal rhythm	Slight dilatation of the vent. system. A little air in the subarachnoid spaces	100/70	220	125/115	Brain tumor? Pleuriglandular syndrome.

KEY: S. A. = Sinus arrhythmia; V. E. S. = ventricular extrasystole; A. F. = Auricular fibrillation; L. V. P. = Left ventricular preponderance; S. T. = Sinus tachycardia.

Results. The results were compiled in the accompanying table.

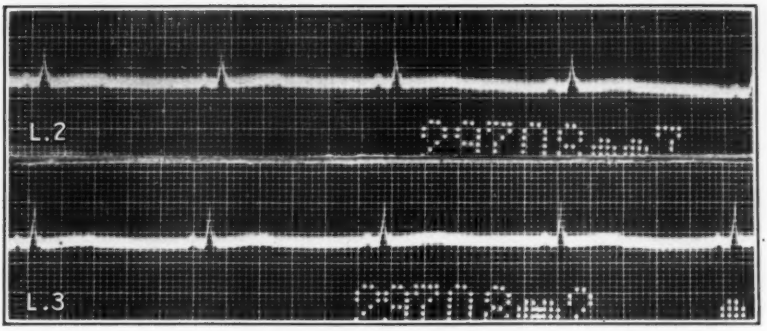


FIG. 1.—Case 2. Lead 2 shows low voltage and bradycardia, and Lead 3 a sinus arrhythmia in addition.

This and the following records were taken during encephalography.

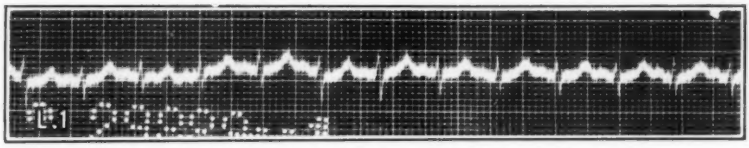


FIG. 2.—Case 7. Sinus tachycardia, 165 per minute.

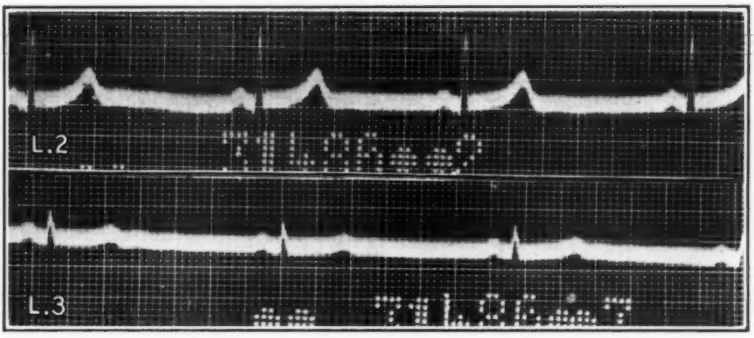


FIG. 3.—Case 11. Sinus bradycardia with R_3 and T_3 lower in Lead 3.

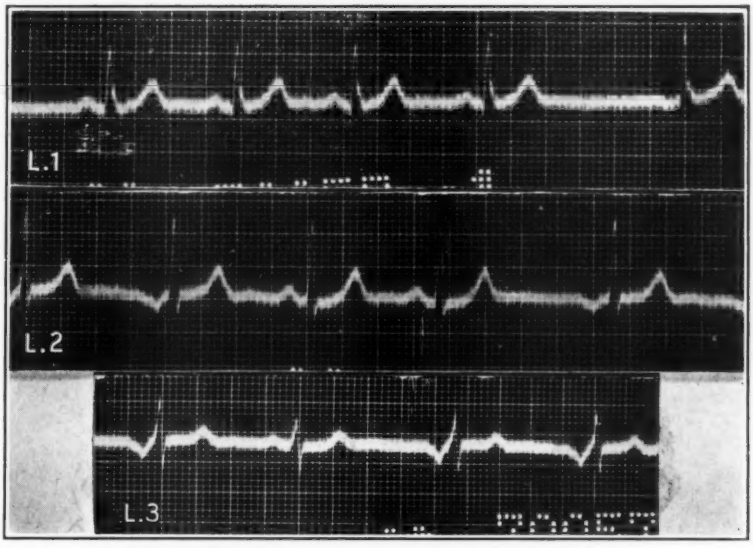


FIG. 4.—Case 9. Records show migration of pacemaker between S–A and A–V node.

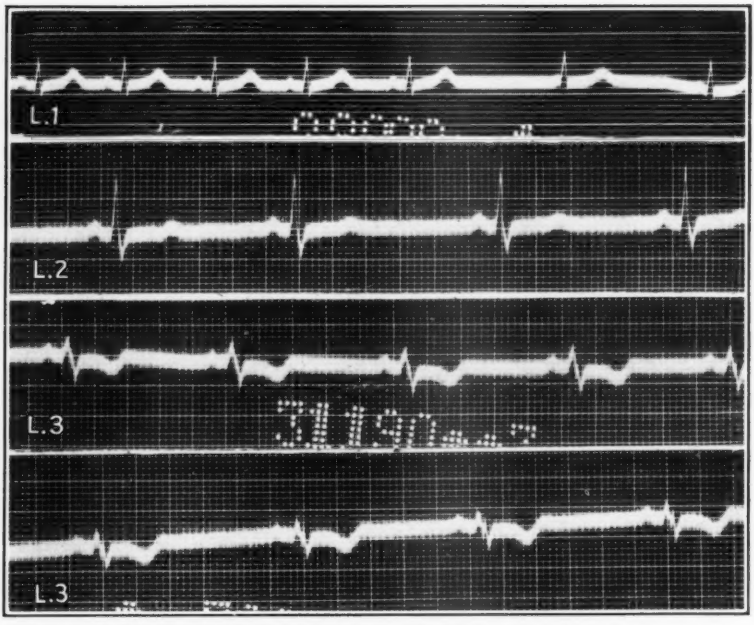


FIG. 5.—Case 13. Lead 1 shows sinus arrhythmia; Lead 2, bradycardia; and Lead 3, notching, T_3 inverted and notching with widening of Q–R–S complex low voltage.

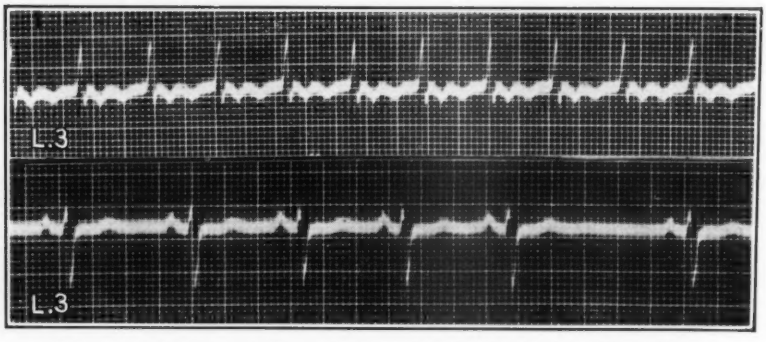


FIG. 6.—Case 14. *A*, Sinus tachycardia; *B*, phasic sinus depression.

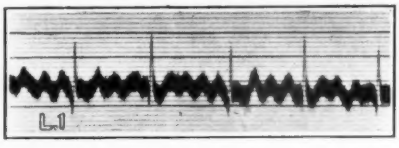


FIG. 7.—Case 20. Auricular fibrillation.

To summarize the results listed in the table it may be pointed out that the most frequent electrocardiographic change was that consequent upon stimulation of the pacemaker, *i. e.*, in 13 cases. Of these, at one or another time during the procedure, 7 showed sinus arrhythmia, 5 showed sinus bradycardia, 2 phasic sinus slowing, 3 sinus tachycardia, and 2 showed a combination of these changes. The next most frequent variations was that consequent upon migration of the pacemaker. Of these, one showed auricular fibrillation (though impure flutter was seriously considered), two showed migration of the pacemaker between the *S–A* and *A–V* nodes. Next in frequency were changes indicative of dominance of the *A–V* node or lower ventricular foci. Of these, there were 3 cases of transitory nodal rhythm and 1 case of ventricular extrasystole. Five cases showed no appreciable change. In 6 cases the bradycardia lasted for 6 hours and then gradually returned to normal.

From these records, the conclusion may be drawn that the majority of the changes are to be attributed to excessive vagus stimulation. This is correlated with the other clinical manifestations of vagus origin. In the 1 case in which auricular fibrillation occurred, this change appeared immediately coincident with the first withdrawal of 15 cc. of spinal fluid, before any air had been injected. What the mechanism in this instance was, we are unable to say. It may have been due to a sudden change in intracranial pressure.

In view of these changes, it is interesting to consider whether or not, interference with the conduction mechanism of the heart might possibly be a factor in encephalography death, especially in those cases where the difference between the amount of fluid removed and air injected is very small and theoretically too little to accommodate air-expansion or air-irritation. The following case of encephalography death is of interest in this connection.

Case Abstract. A man, aged 55, was admitted to the Mount Sinai Hospital on September 29, 1928, with the complaint of weakness in the left upper and lower extremities of 6 months' duration, together with failing vision and personality changes.

Examination. Showed apathy, mental torpor, pyramidal tract signs and weakness on the left side, coarse tremor of fingers of the right hand, and bilateral papilledema and hemorrhages. The blood pressure was 140/85. Laboratory findings were negative. The clinical diagnosis was neoplasm of the right cerebral hemisphere, post-Rolandic in location. Cardiac rate and rhythm normal. Heart sound of poor quality.

Course. On October 5, 1928, at 3.00 P.M., encephalography was performed; 100 cc. of fluid was removed and 100 cc. of air was injected. The patient became ashen and cyanotic. At 6.10 P.M. the pulse was 40. Hands cold. At 11.00 P.M., the patient was in complete coma, breathing stertorously and moribund. The impression clinically at that time was questionably that of hemorrhage into a neoplasm. The next day at 8.20 A.M. the temperature mounted to 107 and the pulse was imperceptible. The patient died 15 minutes later, approximately 17½ hours after encephalography. The left cerebral ventricular system had been well visualized, was displaced to the left and was moderately dilated. The third ventricle was visualized and displaced a distance of ½ inch. No autopsy was obtained.

Inasmuch as anatomic verification of the brain's condition was not possible, it cannot be stated with certainty that there was not a hemorrhage into a neoplasm. However, the lapsing into coma 8 hours after encephalography together with the profound bradycardia and obvious cardiac death makes it necessary to consider the possibility of excessive vagus stimulation in a patient in the sixth decade of life and whose heart sounds were recorded as weak.

Summary. Twenty cases of simultaneous encephalography and electrocardiography are presented with a study of the changes in the cardiac conduction mechanism. The most common changes are those consequent upon stimulation of the pacemaker through the vagus: sinus arrhythmia, sinus bradycardia, phasic sinus slowing, sinus tachycardia, migration of the pacemaker between the *S–A* and *A–V* nodes, transitory nodal rhythm. In 1 case ventricular extrasystole was observed and in another auricular fibrillation. In 1 fatal case following encephalography the death was probably cardiac and followed the excessive injection of air with subsequent bradycardia and collapse at that period when most cases begin to show a return to normal rate. The findings are correlated with other clinical manifestations of vagus stimulation.

We wish to express our gratitude to Dr. I. Roth of the Mt. Sinai Hospital, and Dr. S. P. Schwartz of Montefiore Hospital for their generous coöperation in the reading of the records.

BIBLIOGRAPHY.

1. Krause, F.: Cerebrale Krankheiten des Kindesalters in typischen Encephalogrammen, Ergebn. d. inner. Med. u. Kinderheilk., **37**, 333, 1930.
2. Pancoast, H. K., and Fay, T.: Encephalography: Roentgenological and Clinical Considerations for its Use, Am. J. Roentgen., **21**, 421, 1929.
3. Juzelevsky, A.: Ueber die Gefahren and Komplikationen bei der Encephaloventriculographie, über Prophylaxie und Therapie, Beitr. f. Klin. Chir., **151**, 48, 1930–1931.
4. Meyer, A.: Das Verhalten des Blutdrucks bei der Encephalographie, Klin. Wchnschr., **11**, 1873, 1932.

FURTHER STUDIES IN CALCIUM AND PARATHYROID THERAPY IN CHRONIC ULCERATIVE COLITIS.

By Benjamin Haskell, M.D.,
ASSISTANT IN PROCTOLOGY, JEFFERSON MEDICAL COLLEGE HOSPITAL,
AND
Abraham Cantarow, M.D.,
ASSOCIATE IN MEDICINE, JEFFERSON MEDICAL COLLEGE, PHILADELPHIA.

(From the Proctologic Department of Surgical Division A and the Department of Medicine, Jefferson Medical College Hospital.)

In 1931 we reported[1] the results of calcium and parathyroid therapy and certain observations regarding the diffusibility of serum calcium in a series of 13 patients with chronic ulcerative

colitis. The rationale of this form of therapy was believed to rest upon the beneficial effect of calcium on the following existing conditions: *a*, Nutritional change in the tissues, with or without a disturbance of calcium partition; *b*, spasticity of the colon; *c*, hemorrhage. Eleven of the 13 patients became clinically well in from 4 to 8 weeks and, at the time of the previous report, 10 of these had been observed over a period of from 1 to 2½ years. The mucosa of the lower bowel had resumed a normal appearance in 8, and in 2 symptoms had returned for a short period of time.

In view of the chronic nature of this condition and its marked tendency toward spontaneous remission and relapse, the efficacy of any form of therapy can be properly evaluated only after a prolonged period of observation of individual cases. We have been able to study 8 of the original series of patients over a period of 4 to 6 years and have applied the same therapeutic procedure in 16 additional cases, observed over periods varying from 6 months to 4 years.

Method of Treatment. The plan of treatment is essentially the same as that described in the previous report and includes: (1) a cellulose-free, non-irritating diet; (2) such drugs as belladonna and kaolin; (3) calcium gluconate and parathyroid extract. As was previously emphasized, calcium is best absorbed when the intestinal alkalinity is lowest, and must therefore be administered when upper intestinal digestive activity is at a minimum, *i. e.*, a short time before meals. We believe that neglect of this very important consideration is responsible for many unsatisfactory responses to this form of therapy. Calcium gluconate is administered in doses of 60 grains, 3 to 4 times daily, 3½ to 4 hours after meals. Patients are cautioned to avoid eating between meals. Parathyroid extract (parathormone) is injected intramuscularly, the average adult dose being 20 units. The injections are repeated at intervals of 48 to 72 hours, depending upon the severity of the symptoms.

Clinical Observations. Table 1 contains, in summary form, the pertinent observations made upon the first series of 13 patients, as reported in 1931, and their clinical condition at that time. Ten of the 13 were under observation at the time of the previous report. The subsequent course of these patients is summarized in Table 2. Two have died, 1 of pneumonia (C. T.) and 1 of carcinoma of the descending colon (J. H.); 2 were followed for an additional 2 years but have not been seen for the past 2 years; 6 are still under observation. Eight patients, therefore, have been observed for 2 to 6 years. Of this group, 5 have remained symptom-free for 2 to 6 years; (2, 2 years; 1, 3 years; 2, 6 years); 2 patients (J. E.B. and S.B.) have had remissions of relatively short duration at almost yearly intervals; in 1 case (R. S.) the disease has continued to progress.

The tendency to recurrence is a recognized feature of chronic ulcerative colitis, and it is difficult to determine when, if ever, recovery is complete. Although there may be freedom from all subjective and objective manifestations and a normal appearance

TABLE 1.—SUMMARY OF DATA PRESENTED IN 1931.

Patient.	Age.	Duration of symptoms.	Previous treatment.	Special features.	Duration of calcium treatment.	Period of observation.	Present appearance of mucosa.	Condition since treatment.
J. E. B. . . .	35	8 mos.	Irrigations 3 mos.	.....	6 weeks	30 mos.	Slight congestion	Well.
C. T. . . .	48	8 mos.	Dietetic; sedatives	30 pounds loss in weight and nervous phenomena	8 weeks	24 mos.	Normal	Occasional mucus.
B. O. G. . .	26	10 yrs.	Appendicostomy in fifth year; irrigations	Frequent remissions, longest 4 months	8 weeks	22 mos.	Reddened and thickened	Symptom-free 14 months.
M. A. . . .	41	4 yrs.	Sedative drugs	Lower rectum slow in healing	4 weeks; after 2 mos., 8 weeks	24 mos.	Normal 4 mos. after treatment ended	Tendency toward constipation.
E. d'A. . . .	30	1 yr.	Irrigations; diet; sedatives	Abdominal pain marked	6 weeks	30 mos.	Slight congestion	Occasional mucus in stool.
S. B. . . .	27	2 yrs.	Dietetic	Associated with nervous symptoms	4 weeks	24 mos.	Glazed, pale	Acute attack for 1 week a year later.
J. H.. . . .	54	4 mos.	None	.....	7 weeks	12 mos.	Normal	Return of symptoms after 8 mos.
F. S. . . .	45	4 yrs.	Irrigations	.....	8 weeks	26 mos.	Normal	Occasional mucus.
H. S. . . .	45	12 yrs.	Appendicostomy; normal saline irrigations	Symptom-free 3 yrs. after operation	4 weeks, then discontinued	Not traced	No bleeding ulcers; not entirely healed.	
F. E. . . .	20	7 mos.	None	.....	6 weeks	Not traced	Slightly edematous and granular.	
I. K. . . .	58	3–4 wks.	Rectal instillations	.....	7 weeks	13 mos.	Normal	Well.
R. S. . . .	25	12 yrs.	Dietetic	Remissions 4 mos. yearly almost	3 mos.	10 mos.	No improvement	Bleeding only occasionally; frequency of stool persists.
J. S. . . .	30	3 yrs.	None	.....	1 mo.; discontinued	1 mo.; did not continue	No improvement.	

of the mucous membrane upon sigmoidoscopic examination, remissions sometimes occur after a lapse of years, at times apparently induced by a severe upper respiratory infection or other illness. Two remissions, each of about 2 months' duration, occurred in 1 patient (J. E. B.) while another (S. B.) had several remissions of 3 to 4 weeks' duration at almost yearly intervals; in both cases the response to treatment was comparatively prompt and entirely satisfactory.

TABLE 2.—FOLLOW-UP DATA IN 10 CASES PREVIOUSLY REPORTED AS SUMMARIZED IN TABLE 1.

Patient.	Period observation.	Relapse.	Response in relapse.	Present mucosal appearance.	Present condition.
J. E. B.	6 yrs.	10–1–32 (2 mo.) 11–1–31 (2 mo.)	Slow but complete	Slight congestion	Symptom-free 18 months.
C. T.	3 yrs.	.....	.....	.....	Remained well 3 years; death — pneumonia.
B. O. G.	6 yrs.	10–1–31	Prompt	Atrophic changes	Well; gained 40 pounds
M. A.	4 yrs.	None for 2 yrs.	.....	Normal	Not seen for 1 year.
E. d'A.	6 yrs.	None	.....	Moderate congestion	Irritable colon, no ulceration or bleeding.
S. B.	6 yrs.	Yearly, early winter (2–4 wks.)	Prompt	Glazed pale	Irregular bowel function; occasional frequency.
J. H.	2 yrs.	8 mos. after discharge	.....	.....	Death—polyposis, carcinoma of colon.
F. S.	6 yrs.	None	.....	Slight congestion	Frequent mucus, otherwise well.
I. K.	2 yrs.	.....	.....	.....	Remained well 2 years, not seen since.
R. S.	5 yrs.	Progressively worse	Ileostomy October, 1932 no improvement	Progressive rectal stenosis and bleeding	Unimproved nephritis and anemia.

With the exception of Case R. S. (Table 1) the general condition of the patients in this group has been good, both weight and blood count having returned to normal. Some irregularity of bowel function persists in 2 instances (E. d'A. and S. B.). The former has had attacks of frequency of bowel movement lasting 1 to 3 days, while the latter passes an excessive quantity of mucus. In these patients, the mucous membrane of the bowel has appeared either slightly congested or pale and glazed. Similar changes were present in the bowel in 3 other cases without symptoms and no definite relationship could be demonstrated between the condition of the bowel mucosa and the symptoms exhibited by those patients with mild disturbances of bowel function. The bowel resumed an absolutely normal appearance in only 1 patient, who was, however, under observation for a shorter time than the remainder of this group. In Case R. S., a well-functioning ileostomy resulted in no

improvement in the condition of the colon, Roentgen ray showing extension of the ulcerative process into the ascending colon 1 year after operation. The mucous membrane of the rectum and sigmoid remained extensively ulcerated and friable, with frequent bloody and purulent discharge, and the patient has presented evidence of a progressively advancing nephritis during the past 2 years.

Observations have been made upon 16 additional patients over a period of from 6 months to 4 years. The pertinent data are presented in Table 3. The age incidence, which varied from 14 to 40 years, was as usual for this disease. The average duration of symptoms was 14 months. All presented fairly characteristic changes in the bowel mucosa. Proctoscopic material failed to reveal E. histolytica or other specific organisms, including that reported by Bargen. The period of calcium and parathyroid therapy averaged 7 weeks (3 weeks to 3½ months).

Eight of the 16 patients became entirely symptom-free within 3 to 12 weeks. Of these 8, 4 had short remissions (2 to 4 weeks) which responded promptly to treatment and all have been well for 6 months to 2 years, the bowel having resumed a practically normal appearance upon sigmoidoscopic examination. Of the 16 patients 7 were relieved of their severe symptoms and were restored to fairly good health, with a return of weight and blood count to normal, but with some degree of persistent disturbance of bowel function. Of the 7, 4 suffer with occasional abdominal distress, excessive flatulence and either constipation or increased frequency of bowel movement; they show no evidence of ulceration or bleeding but the mucosa remains somewhat edematous and congested. The other 3 have had persistent frequency of bowel movement, with semiformed stools, but their general condition has been quite satisfactory. Two of these patients were 14 years of age, and in both the condition was more resistant to treatment than in the other individuals in this series. The period of calcium therapy was also longer than in the case of the adults. When first seen, bowel symptoms were severe and both were markedly underweight, with a marked secondary anemia. Blood transfusions and other general measures were employed and, except for the increased frequency of stool, their condition is good at the present time.

One patient failed to respond satisfactorily to treatment (Case 14, L. J.). Bleeding invariably recurred after periods of subsidence of 2 to 3 weeks, and no appreciable improvement followed the institution of other forms of treatment. This patient, who had previously been in apparently good health, began to suffer from marked frequency of bowel movement following two severe emotional shocks in rapid succession. Bleeding was first noted 2 months later, and when first seen extensive superficial ulceration was present. The distressing emotional factors continued to operate and it seemed

that no definite improvement would occur in this case until these factors could be removed.

TABLE 3.—SUMMARY OF DATA IN NEW CASES.

Patient.	Age.	Duration	Special features.	Previous treatment.	Duration calcium treatment.	Period of observation.	Present mucosal appearance.	Condition since treatment.
1. E. P.	14	2 yrs.	Marked weight loss secondary anemia	General dietetic	2½ mos.	18 mos.	Congestion	Irregular bowel function, no bleeding.
2. R. C.	25	2 yrs.	Postpartum anemia leukopenia	General	1 mo. (1) 8 mo. interval (2) 4 mo.	3½ yrs.	Normal	1 remission (1 mo.), symptom-free 12 mos.
3. E. L.	31	7 mos.	Arthritis anemia	Removal focal infection, transfusion	4 wks.	3 yrs.	congestion	Occasional frequency.
4. S. S.	33	2 mos.	Severe abdominal pain, anemia	General transfusion	8 wks.	6 mos.	Edematous	Symptom-free, blood count near normal.
5. R. G.	50	2 yrs.	Remission 3 mos. after onset. Recurrence 1 yr. later	General	1 mo.	6 mos.	Congestion	Symptom-free.
6. R. K.	14	3 yrs.	Perirectal abscesses, fever, loss of weight	General antidiarrhea mixtures	3½ mos.	3 yrs.	Diffusely congested	2–3 semiformed stools daily, occasional blood, weight normal, condition good.
7. J. W.	49	2 yrs.	3–4 stools daily, slight bleeding	None	1 mo.	18 mos.	Normal	Occasional pain and soft stools, no bleeding.
8. M. C.	30	10 mos.	Marked anemia, vomiting	Dietetic transfusion	3 mos.	4 yrs.	Normal	Symptom-free.
9. C. M.	26	2½ yrs.	3–10 stools, slight bleeding	Bargen serum, vaccine, dietetic	3 wks.	16 mos.	Not examined recently	1 brief relapse after 1 yr., condition good.
10. J. C.	29	5 mos.	Marked anemia, constipation	None	3 wks.	3½ yrs.	Dry glazed	Symptom-free, blood count normal.
11. M. K.	25	6 mos.	Marked frequency anemia	General	9 wks.	1 yr.	Congestion, edema	No bleeding, 5-7 stools daily.
12. R. B.	39	18 mos.	Marked bleeding	Dietetic, local	5 wks.	18 mos.	....	Recurrence after 4 mos. Treated 4 wks., symptom-free 1 yr.
13. L. F.	26	5 mos.	Postpartum	Anti-diarrhea mixtures	5 wks.	2 yrs.	Congested granular	1 remission (2 wks.). Occasional symptom of irritable colon.
14. L. J.	36	5 mos.	Long constipation daily laxatives followed emotional upset	Dietetic, medicinal	3 mos.	10 mos.	Granular congested few ulcers	Periodic partial improvement, seldom symptom-free.
15. C. C.	28	6 mos.	Constipation and diarrhea 1 yr. before onset of bleeding	Thyroidectomy, dietetic	10 wks.	18 mos.	Dry glazed	Frequent constipation and flatulence.
16. D. C.	26	3 mos.	Appendectomy 2 mos. after onset, condition worse	Dietetic, medicinal	10 wks.	20 mos.	Congested	1 relapse (3 wks.) following acute respiratory infection.

Discussion. From a clinical standpoint, the favorable therapeutic response to calcium and parathyroid administration noted in the great majority of the cases included in the present report was characterized by rather prompt improvement in two outstanding features of the disease, namely, bleeding from the bowel and colonic spasm and hyperirritability. Cessation of bleeding, which was in most instances the earliest and most constant indication of improvement following the institution of this form of therapy, is, in our opinion, an important factor in bringing about healing of the ulcers. Of perhaps equal importance is the apparently beneficial influence of calcium therapy upon colonic hyperirritability which, with the associated spastic condition of the bowel, must inevitably interfere with healing. Marked reduction in pain and in frequency of stool was noted in several cases in which full doses of belladonna had been ineffectual. It is naturally impossible to state whether healing of the ulcerated areas is predominantly the cause or the effect of the diminished irritability and bleeding. It may be, as suggested in our first report,[1] that calcium favors the healing process directly, by improving the nutrition of the inflamed and edematous bowel wall.

Although the response to treatment was usually prompt in the majority of cases in which favorable results were obtained, definite improvement began in several patients only after parathyroid and calcium therapy had been continued for periods of 4 to 6 weeks, and an adequate response was obtained in 3 patients only after 3 months of continuous treatment. In no instance was any untoward effect observed. It is interesting to note that the response to treatment during relapse in individual cases was almost invariably identical with that observed at the primary institution of treatment. So far as could be determined, those cases in which improvement was prompt and marked differed in no essential respect, either clinically or in the appearance of the bowel, from those which showed no improvement.

Conclusions. 1. Nine patients with chronic ulcerative colitis have been observed for periods of 2 to 6 years after their original course of calcium and parathyroid therapy. Five have remained essentially symptom-free; brief remissions occurred in 2 instances which, however, responded promptly to the same form of treatment. One patient with nephritis and anemia is unimproved and 1 died of pneumonia after remaining well for 3 years.

2. Sixteen additional cases have been treated similarly and have been observed for periods of 6 months to 4 years. Eight became clinically well, 7 were relieved of their severe symptoms and were restored to fairly normal health, with some evidence of persisting colonic irritability, and 1 patient was not benefited.

3. Although the response to treatment is usually prompt, definite improvement occurred in 3 cases only after 3 months of continuous

calcium and parathyroid administration. Cessation of bleeding is the earliest and most constant indication of improvement in the majority of cases.

4. The rationale of calcium therapy in chronic ulcerative colitis is believed to rest upon the favorable influence of calcium upon the following existing conditions: *a*, Nutritional change in the tissues, with or without a disturbance of calcium partition; *b*, spasticity and hyperirritability of the colon; *c*, slow, capillary bleeding.

The calcium gluconate used was supplied through the courtesy of the Sandoz Chemical Company.

BIBLIOGRAPHY.

1. Haskell, B., and Cantarow, A.: Calcium and Parathyroid Therapy in Chronic Ulcerative Colitis, Am. J. Med. Sci., **181**, 180, 1931.

DIABETIC COMA WITH EXTREME HYPERGLYCEMIA.

By Edward S. Dillon, M.D.,
CHIEF, METABOLIC DIVISION, PHILADELPHIA GENERAL HOSPITAL; ASSISTANT PROFESSOR OF DISEASES OF METABOLISM, GRADUATE SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA,

AND

W. Wallace Dyer, M.D.,
ASSISTANT CHIEF, METABOLIC DIVISION, PHILADELPHIA GENERAL HOSPITAL, PHILADELPHIA, PA.

(From the Metabolic Department, Philadelphia General Hospital.)

Our interest in this subject was aroused by a recent patient whose blood sugar was 1850 mg. and who recovered. Recovery in cases of diabetic coma with extreme hyperglycemia is not common, but the literature does contain a few reports.

Marble, Root and White[1] reported that 10 cases had been encountered at the George F. Baker Clinic with blood sugars of 1000 mg. or more, of which 6 recovered and 4 died. Curtis and Dixson[2] previously reported 1 case of this group which had a blood sugar of 1620 mg. and recovered. Kehr and Kocher[3] reported a case with a blood sugar of 1028 mg.; Gray and Sansum,[4] a case with a blood sugar of 1000 mg.; Shepardson and Anderson,[5] a case with a blood sugar of 1090 mg.; and Foster,[6] a case with a blood sugar of 1260 mg. All of these cases recovered.

Higher blood sugars have been reported in cases which died. Lawrence[7] reported a case which he treated, in 1930, with a blood sugar of 2060 mg. 2 hours after 40 units of insulin had been given. Argy[8] reported a case with a blood sugar of 1710 mg. without acetone in the urine; and Pitfield[9] had a case with 1700 mg.

We are presenting the records of 16 cases of diabetic coma in

which the blood sugar was 1000 mg. or more at admission to the wards of the Metabolic Department, Philadelphia General Hospital.

TABLE 1.—CASES OF DIABETIC COMA IN WHICH THE BLOOD SUGAR WAS 1000 MG. OR ABOVE.

Case.	Name.	Age.	Sex.	Race.	Date.	Admission.	Blood sugar (mg.).	CO_2.	Urea N.	Outcome.
1 . .	T. J.	40?	M.	B.	11/23/25	First	1520	21	..	Died 3 hrs.; autopsy.
2 . .	M. M.	58	F.	W.	4/ 2/26	First	1120	..	45	Recovered.
3 . .	T. M.	27	M	W.	1/12/27	Fifth	1484	11	..	Died 8 hrs.
4 . .	E. T.	50	F.	B.	7/19/28	First	1060	8	30	Died 16 hrs.; autopsy.
5 . .	H. H.	30	F.	B.	3/30/29	First	1080	11	21	Recovered.
6 . .	G. M.	28	F.	B.	12/11/29	First	1030	12	50	Died 25 hrs.; autopsy.
7 . .	J. J.	35	M.	B.	1/29/30	First	1500	24	..	Died 8 hrs.; autopsy.
8 . .	H. H.	31	F.	B.	5/14/30	Second	1056	10	..	Died 6 hrs.; autopsy.
9 . .	C. R.	46	F.	B.	6/12/31	First	1056	18	55	Recovered.
10 . .	S. D.	20	F.	W.	9/11/31	Seventeenth	1000	16	..	Died at admission.
11 . .	L. J.	53	F.	B.	6/10/34	First	1028	12	..	Died 2 hrs.; autopsy.
12 . .	M. H.	54	F.	B.	10/ 5/34	First	1008	22	95	Died 59 hrs.; autopsy.
13 . .	M. S.	40	F.	W.	10/ 9/34	Sixth	1000	7	20	Died 16 hrs.
14 . .	N. D.	21	F.	B.	12/23/34	First	1850	13	95	Recovered.
15 . .	F. C.	39	F.	B.	1/20/35	First	1024	15	63	Recovered.
16 . .	S. P.	56	F.	W.	2/28/35	First	1470	10	42	Died 2 hrs.; autopsy.

These cases occurred among 3461 admission to this department up to March 1, 1935. Three of these cases (Nos. 2, 5 and 9) have been reported previously by Haines and Davis.[10]

Of the 16 patients, 5 recovered and 11 died; 13 were women and only 3 were men. There were no children. We were astonished to find that 11 were negroes. According to the 1930 census, negroes constituted 11.3% of the population of Philadelphia. Of all the patients admitted to the hospital, 28.5% are negroes, and of those admitted to the Metabolic Department, 20% are negroes.

Of these cases, 12 were previously unknown to this department. Cases 5 and 8 were the same individual. Three patients (Nos. 3, 10, 13) were chronic offenders. Patient 10 was admitted to the department 17 times in 3 years, twice with a CO_2 of 6, 8 times with CO_2 of 11 to 20, 5 times with CO_2 of 21 to 27, and twice with a normal CO_2.

Patient 12 had severe gangrene of a foot and leg. A thigh amputation was performed 19 hours after admission, at which time the blood sugar was 520, CO_2 56, urea nitrogen 60. She died 40 hours after the operation.

Patient 16 had extensive gangrene of both feet.

We are reporting Patient 14 in detail, because we have not seen in this clinic, nor have we been able to find in the literature, a similar case of hyperglycemia with recovery.

Case Report. N. D., aged 21, colored female, was first admitted to the Philadelphia General Hospital, June 27, 1934, at which time she was delivered at term of a living female child. Four urine examinations were negative at this time for sugar. Because of a minor infection in the episiotomy wound, the patient was not discharged until July 20, 1934, at which time she and the baby were in good condition.

TABLE 2.—DETAILS OF COURSE AND TREATMENT OF CASE 14.

	Time.	Blood sugar.	Urea N.	CO_2.	Hemoglobin. W. B. C.	Blood pressure.	Insulin.	Saline.	Glucose, gm.	$NaHCO_3$, gr.	Acacia, gm.	Cholesterol.	Whole blood chlorid.	Blood sulphur.	Urine.
12/23/34	4:30 P.M.	1850	95	13	16.8	30/0	280	500	..	160	30				
	7:00 P.M.	1550	..	13	12,700	82/30	200	2000	..	120	..	170	430		
	9:00 P.M.	1280	..	18	....	70/30	100	500	..	..	30	..	..	8	
	12:00 P.M.	896	..	32	....	74/30	80	2000	90	120	..	..	..	..	400 cc.
															Cath.
12/24/34	3:00 A.M.	720	..	47	....	76/40	..	1500	..	..	..	..	..	..	90 cc.
	6:00 A.M.	610	..	48	13.1	84/42	..	..	..	..	..	..	460	..	250 cc.
	8:00 A.M.	488	79	56	9,800	86/34	..	2000	30						
	10:00 A.M.	544	..	56	....	88/68	30								
	12:30 P.M.	360	..	54	....	90/64	20	250	50	..	..	..	..	..	500 cc.
	7:00 P.M.	268	..	61	....	90/64	..	..	..	..	..	..	..	..	700 cc.
	12:00 P.M.	302	..	..	....	..	3	..	..	..	..	..	..	..	750 cc.
12/25/34	7:00 A.M.	266	33	57	....	..	..	..	..	..	..	..	..	..	950 cc.
1/31/35*	7:00 A.M.	159													

* Diet: P., 60; F., 130; C., 140. Insulin: 10–0–0. Twenty-four-hour urine sugar, negative.

Following discharge she was well until December 9, 1934, when she became increasingly weak, until December 21, when she became delirious. She was admitted to this department, December 23. The patient was semiconscious and extremely restless; temperature 96° F. (rectal), pulse imperceptible, respirations 36. The respirations were not typically Kussmaul. The physical examination were essentially negative, except for soft eyeballs, inaudible heart sounds and blood pressure of 30 systolic and 0 diastolic.

Blood studies at 4.30 P.M. showed blood sugar (Folin-Wu) 1850 mg. (checked), urea nitrogen 95 mg., CO_2 13 vol. %. The progress and treatment can be followed best in Table 2. Sixteen hours after admission the patient was completely conscious and oriented. On December 25, 1934, the patient took a liquid diet of protein 60 grams, fat 130 grams and carbohydrate 140 grams.

Five days after admission her temperature rose and the left chest showed physical signs of lobar pneumonia. This was substantiated by roentgenogram. Her convalescence was slow, but uneventful, the temperature coming to normal on the 17th day. She was readily standardized on a diet of protein 60 grams, fat 130 grams, carbohydrate 140 grams and 10 units of insulin before breakfast.

Of interest in this patient was the exceptionally high initial blood sugar and the profound state of "medical shock" on admission. The response to treatment was rapid and continuous.

A total of 660 units of insulin, 6500 cc. of normal saline solution, 400 grains of sodium bicarbonate, 60 grams of acacia, 90 grams of glucose were given in 12 hours.

The plasma cholesterol $2\frac{1}{2}$ hours after admission was 170 mg., of which 82 mg. (48%) was ester. The whole-blood chlorid, taken at the same time, was 430 mg. and the blood sulphur was 8 mg. Seven days later the plasma cholesterol was 112 mg., ester 43 mg. (38.4%), the sulphur 1.2 mg., and the whole-blood chlorid 520 mg.

The Kahn reaction was negative.

All blood analyses during this coma were done by Mr. T. V. Letonoff, Chief Chemist of this clinic.

Summary. Sixteen cases of diabetic coma are reported which had blood sugars of 1000 mg. or above at admission to the hospital. One patient had a blood sugar of 1850 mg., the highest on record in which recovery occurred.

REFERENCES.

1. Marble, A., Root, H. F., and White, P.: Diabetic Coma, New England J. Med., **212**, 288, 1935.
2. Curtis, W. S., and Dixson, I. M.: Extreme Hyperglycemia in Diabetic Coma With Recovery, J. Am. Med. Assn., **90**, 1115, 1928.
3. Kehr, E. F., and Kocher, R. A.: Marked Hyperglycemia in Diabetic Ketosis and Beginning Coma With Recovery, California and West. Med., **38**, 371, 1933.
4. Gray, P. A., and Sansum, W. D.: Diabetic Coma With Marked Hyperglycemia and Recovery; Report of a Case, J. Am. Med. Assn., **97**, 230, 1931.
5. Shepardson, H. C., and Anderson, E. M.: Diabetic Coma With Marked Hyperglycemia and Recovery; Report of a Case, Endocrinology, **13**, 188, 1929.
6. Foster, N. B.: Diabetic Coma, J. Am. Med. Assn., **84**, 719, 1925.
7. Lawrence, R. D.: Extreme Hyperglycemia in Diabetic Coma, Brit. Med. J., **1**, 377, 1934.
8. Argy, W. P.: Hyperglycemia (1.71 Per Cent) With Coma; Associated With Absence of Acetone in Urine, Boston Med. and Surg. J., **193**, 1236, 1925.
9. Pitfield, R. L.: Unusually High Blood Sugar Content in Case of Diabetes, Med. J. and Rec., **120**, 433, 1924.
10. Haines, C. J., and Davis, R.: Diabetic Coma With Blood Sugars Above 1000 Milligrams; Report of 3 Cases With Recovery Following Treatment, J. Am. Med. Assn., **99**, 24, 1932.

THE METABOLISM OF GALACTOSE.*

III. The Influence of Disturbed Endocrine Function.

By Allan Winter Rowe, Ph.D.,
DIRECTOR OF RESEARCH, EVANS MEMORIAL, BOSTON, MASS.

(From the Evans Memorial, Massachusetts Memorial Hospitals.)

In a series of earlier papers,[1] the author and his associates have presented the results of investigation on the influence of a variety of agencies upon the capacity of the human organism to utilize galactose.† That disturbed function of the several endocrine glands exercises a profound influence on carbohydrate metabolism has long been recognized. An extensive literature on the topic exists, and includes the description of numerous efforts to utilize this fact for the diagnosis of disorders of the ductless glands. Equally, it has been known that disturbances in sugar metabolism may arise from an even larger number of non-endocrine causes, and these, too, have received due investigation and report. The determination

* This and the following paper had been completely prepared for publication before Dr. Rowe's death, in December, 1934.

† An earlier survey of the present topic was accepted and held for publication by a journal which has since been discontinued. As interest in the metabolism of this sugar has been recently reawakened, the present material has been collated, incorporating certain of the newer ideas and drawing on a more extensive material.

of the so-called carbohydrate tolerance as evidence of disease constitutes a frequently advocated diagnostic procedure and one the validity of which is denied with equal frequency. The conditions of application of the test and the interpretation of results are almost as numerous as the articles describing them. One principal cause of conflicting reports is a seeming failure to recognize that the application of the test leads to the measurement of a single end result common to a wide variety of causes. Further, there may coëxist in the single organism two or more agencies, each capable of influencing sugar utilization, producing reinforcement or antagonism, and that the tolerance as measured is the algebraic sum of these several factors. The crucial experiments of Houssay[2] and Barnes[3] leave no doubt as to the validity of this fact so far as ductless glandular agencies are concerned; these and other factors will be considered in the body of this paper. Failure to make due allowance for the carbohydrate paradox (Allen[4]) and the limitation of the quantitative significance of the blood-sugar curve are among the other factors which have produced completely contradictory interpretations. For the above and similar valid reasons, no review of the literature will be presented; citations as they occur are solely expository to the text, offering the interested reader access to additional detail.

For purposes of this study, we have adopted the original Hofmeister[5] technique, *i. e.*, the use of a series of graded test meals with the production of a transitory galactosuria as the index of an exceeded limit of utilization. The method of application of the test has been discussed at length in the earlier papers[1] and need not be repeated here.

The cases utilized for this study had all received a comprehensive clinical and laboratory study during a period of not less than 7 days' hospitalization,[6] and the diagnoses were derived from the integration of all of these resulting evidences, each interpreted in terms of all other pertinent data. Effort was made to ascertain all departures from the physical normal presented by the individual with a just recognition of the possible misleading influence of unrecognized superimposed effects.

The cases have been selected, so far as possible, to eliminate those complications which could and do independently influence carbohydrate metabolism. The results from such superimposed effects, in those few cases presenting them, and which for a variety of reasons have been included in the series, will be discussed at the appropriate point in the text.

A series of 1000 cases has been selected for this survey, comprising patients with the various types of disturbed function of the pituitary and thyroid, supplemented by series of ovarian and pancreatic failure, and a small group with hypofunction of the adrenals. The partition among the several etiologic entities is given in Table 1.

TABLE 1.—COMPOSITION OF GROUP.

Gland.	Function level.	Number.
Pituitary	Hyperfunction (+)	10
	Dysfunction (±)	300
	Hypofunction (−)	150
Thyroid	Hyperfunction (+)	25
	Dysfunction (±)	75
	Hypofunction (−)	150
Ovary*	Hypofunction (−)	250
Pancreas	Hypofunction (−)	30
Adrenal	Hypofunction (−)	10
		1000

* Functional failure, 225; castrates, 25.

A few words as to the basis of selection is called for.

The pituitary, thyroid and ovarian groups show a numerical relationship which is approximately that of their appearance in the diagnostic clinic. That the figures are influenced by this origin is certain, and as a statistic cannot be interpreted in terms of usual frequency of incidence in the community. Hyperpituitarism and hyperthyroidism find but scant representation, largely because these conditions in an established state do not call for an elaborate diagnostic survey and are referred primarily for treatment. The figures for the dysfunctional and hypofunctional stadia are more nearly characteristic, since their somatic evidences are less distinctive and as a medical rather than a surgical approach is the therapy of election. Likewise, the diabetics are cases for treatment rather than for an elaborate diagnostic approach; the adrenal cases do no more than reflect the rarity of established adrenal failure. The testicle has been omitted as the adult male castrate presents a normal sugar metabolism, and we are lacking objective evidence of any significant endocrine influence of these glands in the adult human.[7] The parathyroids have also been excluded, in largest part from a dearth of suitable material. The statement has been occasionally—and somewhat loosely—made that parathyroid failure lowers the sugar tolerance. This seemingly derives from animal experiments; Falta,[8] who reports this phenomenon with parathyroidectomized dogs, could not duplicate it in cases of idopathic tetany in man. Erdheim,[9] using galactose (40 gm.) and blood-sugar curves, could find no lowering of tolerance in idiopathic tetany; on the other hand, he interprets his results to indicate a probable moderate increase. Our few cases of osteitis fibrosa cystica have presented disturbing complications which have precluded the certain estimation of the parathyroid influence.

Before discussing the numerical data, certain terms must be defined for the sake of clarity. Hypofunction is that picture produced by ablation of the gland or by its known definitely depressed hormone production. Hyperfunction, naturally the antithesis so far as hormone production is concerned, is recognized in this series

only in the thyroid and pituitary groups. While all aberrant activities are dysfunctions, this latter caption has been reserved, for classificatory purposes, to those conditions in which evidences are presented simultaneously in the same subject of both overactivity and underactivity. In the case of the thyroid, one is certainly dealing with a transitional state sometimes evoked by surgery, more frequently, in this series at least, by spontaneous sequential functional depression. With the pituitary, yet other permutational elements enter in as there are two well-differentiated lobes; the pars intermedia is believed by many to constitute a third functional entity, and the infundibulum, remotely, may constitute a fourth. Dysfunction, then, of this composite gland may include any of the rather numerous possibilities of inequality of functional level, together with a true transitional status. The usual formula of objective evidences includes, among others, a lowered basal rate and sugar tolerance, although the opposite condition may obtain. We have been privileged through the years to observe a small number of cases which, starting at an initial level of hormonal overproduction, have escaped surgery, and through the years have declined gradually to a terminal hypofunction. As early as 1911, Cushing and his associates[10] reported this sequence in the carbohydrate metabolism of a series of pituitary cases.

Certain general data, either defining the individuals composing the group or bearing directly on their general sugar metabolism, have been collected.

TABLE 2.—PITUITARY.

Datum.	Function.			Average or total.
	+	±	−	
Male	4	85	41	130
Female	6	215	109	330
Age, low, yrs.	19	4	7	
high, yrs.	63	68	71	
average, yrs.	38.8	31.8	30.6	31.5
Glycosuria, %+	50.0	17.0	0	
Blood sugar, low, mg.	86	72	72	
high, mg.	100	115	119	
average, mg.	93	91	94	92

Broadly speaking, the females outnumber the males in a proportion of 5 to 2. The ages show a wide range between individuals, but a nearly constant average in the two groups of appreciable proportions. Half of the hyperfunctional and none of the hypofunctional group show glycosuria, with an intermediate value for the group of dysfunctional cases. The blood-sugar values show nothing remarkable other than the fact that so many individuals with normal blood sugars demonstrate a slight but definite glycosuria. This is certainly a reflection of a disturbed carbohydrate metabolism which cannot be solved by the convenient postulate of a "renal glycosuria," and which leaves the fundamental question still in abeyance.

TABLE 3.—THYROID.

Datum.	Function. +	Function. ±	Function. −	Average or total.
Male	9	11	50	70
Female	16	64	100	180
Age, low, yrs.	6	8	5	
high, yrs.	58	66	71	
average, yrs.	36.4	27.4	24.4	26.5
Glycosuria, % +	28.0	12.0	4.0*	
Blood sugar, low, mg.	80	73	71	
high, mg.	111	120	118	
average, mg.	92	96	92	93

* Four cases with no demonstrable complication, 1 psychosis and 1 gonorrhea.

The sex division in the thyroid group shows almost identically the same average as did the pituitary. There is a definitely lesser uniformity throughout the three functional subgroups with the dysfunctional series showing but 1 male in 7. The explanation is not forthcoming. The ages show a decline as one progresses toward lessened function; this is undoubtedly due in part to the relatively large number of children studied who presented a thyroid failure dating from early childhood.

Glycosuria in the overactive group is but half as frequently recorded as in the equivalent pituitary moiety. The dysfunctional figures more nearly concur with those of the hypophysis, and even the hypofunctional fraction shows a modest number of patients with glycosuria. Two of these had complications which were possibly the causal agents; the other 4 did not, and it seems probable that they were transitional cases, the glycosuria being the sole persistent residuum of their earlier hyperactive state. The blood sugars, as in the case of the pituitary, show nothing remarkable, all falling within the limits of the conventional normal zone. From the figures as quoted, it is permissible to infer that the influence of the thyroid on carbohydrate metabolism, while considerable and operating in the same sense, is certainly less than that of the pituitary.

As the other endocrine structures under discussion present but one level of functional activity, their data can be combined in Table 4. Allowance is made in the diabetic group for those presenting a picture modified by insulin therapy.

TABLE 4.—OTHER ENDOCRINE GLANDS.

Datum.	Ovary.	Pancreas. Insulin.	Pancreas. Untreated.	Adrenal.
Male	0	10		3
Female	250	20		7
Age, low, yrs.	14	11		22
high, yrs.	68	70		61
average, yrs.	34.7	50.3		35.7
Glycosuria, % +	23.0	75	100	40.0
Blood sugar, low, mg.	75	81	158	74
high, mg.	118	173	334	85
average, mg.	94	118	234	79

All of the ovarian cases had matured; the series average falls but slightly above that of the pituitary group. One-fourth of the series showed glycosuria, while the blood-sugar values were entirely normal. It may be said in passing that the higher levels of blood sugar recorded throughout the first three major groups not improbably reflect a nervous response to venipuncture; this is certainly the case with a number of the oversensitized individuals with ovarian failure. With the pancreatic group, the sex proportion approximates that of the pituitary and thyroid series, and the same is true for our few adrenal cases. The diabetics are distinctly older as a group, although the age scatter is substantially that of the other series. The youngest adrenal case was 22 years; the average age falls in the middle of the fourth decade.

As was to be anticipated, glycosuria of a marked degree characterized the diabetics, but a few insulinized patients being sugar free. A high incidence (40%) was also found in the adrenal group. As was noted a number of years ago,[11] the earlier reports of an increased tolerance in Addison's disease in large measure derived from an erroneous interpretation of animal experiments and the general response to suprarenin. The two groups of pancreatic cases exhibit blood-sugar levels determined by their relative therapeutic status. The adrenal blood sugars show a trend toward that hypoglycemic level which is now generally recognized as characteristic of the condition.

To summarize briefly, glycosuria appears through the entire series with significant frequency with the exception of the pituitary failures and, in nearly equal measure, those of the thyroid. Blood sugars are normal except in diabetes where the hyperglycemia is pathognomonic, and in the adrenal group where the converse is almost equally typical.

Before reporting the results of the galactose testing, a few words as to standards are essential. While the normal healthy male seemingly responds to a dose of 30 gm. irrespective of age, the female shows a fluctuation seemingly intrinsic in her several levels of sexual maturity and activity. While the question has been discussed at length in the earlier papers, a brief review may be permissible for purposes of later orientation. The normal healthy prepuberal child responds to 20 gm. With the onset of menstruation, the level rises and in the course of the first year usually attains the adult standard of 40 gm. Menstruation and pregnancy tend to lower this adult level, the latter ultimately to the prepuberal standard of 20 gm., followed by gradual recovery to the adult plane after delivery. Castration likewise, after a period of adjustment, will produce a consistent prepuberal tolerance (v.i.). The writer has suggested in this a possible mammary influence and has offered certain documentation to support this thesis. Certainly in the adult female, free from complications which might affect sugar

metabolism, removal of the breasts drops the galactose tolerance from 40 to 20 gm. An interesting, indirect support is found further in the observation (unpublished data) that the adult tolerance for levulose is unaffected by ablation of the mammary glands in the human female.

Reverting to the definition of standards, the menopause seemingly produces some degree of retrogression in galactose tolerance, but without the uniformity that characterizes the other stadia. About two-thirds of the postmenopausal women respond to 30 gm.; the remainder retain the 40-gm. level of the normal adult.

It should perhaps be noted that the 10-gm. intervals mentioned in the preceding discussion do not imply abrupt transitions, but represent the conventional levels used in applying the test.

With the female standards dependent upon the levels of sexual activity, tolerance variations throughout the series can be equated only by expressing them in relative terms of departure from that normal which is appropriate to the individual. The same impediment does not exist with the male, but for purposes of uniformity in reporting, the same convention is adopted. The postmenopausal female introduces a difficulty in that seemingly normal individuals respond severally to both 30 and 40 gm. As a partial solution to the question, both of these levels are reported as normal (deviation ± %) in the subsequent tables, and departures from these two levels are calculated on the basis of a mean postmenopausal level of 35 gm. The possible arithmetical errors introduced by the adoption of this convention are of minor magnitude, and with the small percentile representation of the cases requiring its use, the data are readily absorbed into averages which are no more than a first approximation. Further, an analysis of these postmenopausal cases constitutes a portion of this report, the data demonstrating the warrant of the convention adopted.

Turning now to the actual results of the tolerance testing, the data from the pituitary series have been collected in Table 5.

TABLE 5.—GALACTOSE TOLERANCE. PITUITARY.

Tolerance.	Hyperfunction, per cent.	Dysfunction, per cent.	Hypofunction, per cent.
High	−25	±0	+350
Low	−87	−87	±0
Above normal	0	0	98
Av. deviation	—	—	+73
Normal	0	3.7	2
Below normal	100	96.3	0
Av. deviation	−58	−51	—
Group deviation	−58	−49	+71

As will be seen, all of the hyperfunctional cases show a depressed tolerance, with an average deviation reaching the significant amount of −58%. In the large dysfunctional series, a few presented normal tolerances, but the great majority exhibited a depression of

the capacity of utilization for galactose, which in many cases, was of very marked degree. Fifteen of the earlier cases responded to a test meal of 5 gm.; in the more recent applications of the test, in the interest of economy of time for the patient, 10 gm. has been the smallest dose exhibited. All of these cases showed a definite lowering of the respiratory metabolism from normal standards.

With pituitary failure, there is a complete change in the sign of the departure from normal tolerance, and the deviations are even more pronounced than in the other two categories. It must not be forgotten, however, that there is a definite arithmetical limit to depressed values which does not operate in the zone of increased tolerance. Only 2% of this group showed a normal level, none were below and the average departure for the group, the considerable amount of +71%. However and through what agencies the effect be mediated, there can be no question but that the pituitary exercises a profound influence on sugar metabolism. Further, there is no other recorded agent which will produce the massive increases in tolerance which are characteristic of pituitary failure.

Leaving the hypophysis for the moment, the data from the thyroid series present:

TABLE 6.—GALACTOSE TOLERANCE. THYROID.

Tolerance.	Hyperfunction, per cent.	Dysfunction, per cent.	Hypofunction, per cent.
High	±0	±0	+100
Low	−75	−75	±0
Above normal	0	0	**12.0**
Av. deviation	—	—	+43
Normal	**4.0**	**33.3**	**88.0**
Below normal	**96.0**	**66.7**	0
Av. deviation	−60	−33	—
Group deviation	**−58**	**−22**	**+5**

Uniform with the pituitary in sense and direction, the hyperthyroid group shows no case with augmented tolerance. One patient was normal, and the remainder all exhibited varying degrees of depression. The group average fortuitously is identical with that of the equivalent pituitary subseries. The composing members were all definitely toxic, and transitional types (with the possible single exception) have been excluded. The clinical and laboratory pictures were typical; so far as is known, all of the cases in this series were operated upon subsequent to the study, but we have not complete data as many came from a distance and returned to their homes on completion of the diagnostic survey.

The dysfunctional moiety equally show no cases with increased tolerance, but one-third were normal, and the average depression of the utilization capacity of the group is of very modest proportions. Many of these were cases examined after operation and presented the characteristic irregularities in rapidity of the decline of objective evidences toward a normal or terminal hypofunctional level.

The established thyroid failures show a slight upward tendency of the tolerance which in isolated cases may assume really significant proportions (+100%). In the main, however, the effect on the carbohydrate metabolism is not marked, and 88% of the entire group yielded normal tests. If the degree of depression of the basal rate may be taken as a rough index of the lowering of glandular activity, the report of a single case in the series may be quoted in support. The patient was a man in his early sixties, with a long-standing and severe myxedema, and a basal rate 60% below his predicted normal. The blood and urine pictures gave evidence of definitely lowered renal permeability. He was positive with 50 gm. of sugar, or a deviation of +67%. The case with the tolerance increase of +100% reported in Table 6 was also an aged person with severe myxedema and renal impairment. As was noted above, the evidence indicates that the thyroid exercises a considerable influence on sugar metabolism in the same sense as does the pituitary but falling far short in degree of the effect of the latter. Some of the more recent work on intermediating hormonal influences between these two incretory structures may hold suggestions of an underlying mechanism. Discussion of these highly interesting matters, however, can find no place in the present statement.

In presenting the material from the examinations with the remaining endocrine groups, for initial presentation no difference is made between the ovarian failures of functional and those of surgical origin. True, it is known that removal of the sex glands in woman lowers her galactose tolerance to the prepuberal level, and that thus 20 gm. is her normal tolerance. She is an abnormal individual, however, and our primary effort is to ascertain the influence of abnormalities upon the sugar levels which characterize the normal, intact, adult female. The castrate group will have brief individual notice later in the text.

TABLE 7.—GALACTOSE TOLERANCE. OTHER ENDOCRINE GLANDS. (HYPOFUNCTION.)

Tolerance.	Ovary, per cent.	Pancreas, per cent.	Adrenal, per cent.
High	±0	±0	−25
Low	−87	−75	−87
Above normal	0	0	0
Av. deviation	—	—	—
Normal	**2.8**	**13.3**	0
Below normal	**97.2**	**86.7**	**100**
Av. deviation	−47	−55	−62
Group deviation	**−45**	**−48**	**−62**

Here, in opposition to the two glands previously discussed, lowered functional activity determines a depression in tolerance of wholly significant proportions and operating certainly in 97% of the group of ovarian failures.

Lowered tolerance is to be anticipated with the diabetics, and

the present data offer no decided negation to the general trend. It is to be noted, however, that 13% show normal tolerances for galactose, and these are all in the untreated group. Further, the insulin influence in this small series is seemingly not a serious factor in determining the individual levels. Twelve cases were under insulin therapy, and their average deviation was −53% as against that of the 18 untreated cases which was −45%. Several explanations at once suggest themselves, the first and most probable being that the two groups are too small for the arithmetical values to have any precise significance. It might be argued further that the more severe cases were those under therapy, but an analysis of the case records fails to yield an unqualified support to this explanation. Several recent investigators[12,13] have reported that insulin has no effect on the utilization of galactose (direct effect would be implied here), and our present small series certainly presents results that are not inharmonious with this report. There is, further, a recent literature, in part advocating the use of galactose by the diabetic, and in part denying its utility. Without entering the controversy, it may be said that the present figures offer some slight support to the first contention, as the utilization shown here is as good, or better, than in a number of the other endocrine conditions here reported. Too sweeping an inference should be avoided, (1) because of the small number of cases, and (2), since the mechanisms involved are patently different, the diabetics being the only cases exhibiting hyperglycemia.

The adrenal cases show an unvarying depression of galactose tolerance and one of the same order of magnitude as the extreme conditions of overactivity in thyroid and pituitary. The findings here are diametrically at odds with the usual statement concerning adrenal influence on sugar tolerance. There is a voluminous literature in this field, and practically all writers seem to concur in the opinion that adrenal failure produces an increase in the tolerance. The great majority of the studies, from which this opinion derives, are based upon the influence of suprarenin injections on the level of blood sugar, or less frequently on the production of glycosuria, procedures outside the range of this discussion. Of the very few studies which are comparable to the present investigation, Eppinger, Falta and Rüdinger[14] state that they found a very high tolerance for sugar in 3 cases of Addison's disease, while numerous writers have reported the low blood-sugar curves which are considered indicative of an increased assimilation limit. A single exception is in a recent paper from Porges and Adlersberg,[15] in which they report marked transitory hyperglycemia in Addison's disease after glucose feeding, a finding suggesting, though not certainly defining, a lowered utilization capacity.

In contradiction to this mass of opinion, all the cases in this series showed a depressed tolerance for galactose. Question as to

diagnosis is answered by the fact that in the typical cases, primary adrenal involvement was verified at autopsy. Kidney lesions seem to be the almost invariable complement of adrenal disease. The contradictory results of the other observers already cited may be due to lessened kidney permeability, possibly to the fact that galactose was not the sugar used, or possibly to other and unknown causes. The frequently observed hypoglycemia of adrenal failure has been confirmed in the present group. This might influence the so-called tolerance if determined solely by the character of blood-sugar curves without observation of the urine changes. As before stated, sugar anomalies produced by epinephrin injection fall outside the scope of the present discussion, as presumably they include a mechanism differentiated from that operated by the oral administration of sugar.

There remain yet a few additional matters which must be touched upon briefly. In the opening portion of this paper, comment was passed upon the well-known fact that a variety of agencies, not directly associated with ductless glandular activity, play definite parts in influencing sugar metabolism. Further, it was noted that, in largest measure, endocrine cases presenting such complications had been excluded from the present study series. Finally, attention was called to the demonstrable fact that where two such agencies operate in the same individual, the observed end result is an effect presenting the algebraic summation of their several influences. To illustrate these points and to touch upon other matters as well, two groups have been selected, one, a series of 25 castrates from within the body of the study group, the other, an appended series of 50 cases of thyroid failure complicated by hepatic dysfunction. The association presented in the second group is of fairly common occurrence and has already been described.[16] Turning first to the castrates, it may again be noted that removal of the ovaries ultimately lowers the galactose tolerance to the prepuberal level of 20 gm. Time is necessary for readjustment, and the terminal condition does not appear at once. In a brief series now being studied in another connection (unpublished data), all of the composing members of which had been castrated less than three weeks before the study, 4 gave a positive response to 30, 3 to 20 and 2 to 10 gm. of galactose. One of the 2 with the low (10-gm.) tolerance had had a dermoid cyst in addition to a uterine malignancy, the other a chronic oöphoritis of long standing. Both of these influences could complicate the picture. Turning to Table 8, we find that 4 of the group had tolerances 10 gm. above that conditioned directly by their ovarian status. They were all aged women, castrated many years previously, and all had objective evidences of an established nephritis with a lowering of renal permeability. Four others in the group showed abnormally low tolerances, and all of these were syphilitic, a condition well known to influence the

carbohydrate metabolism. The uncomplicated cases all were in harmony with prediction; the 4 luetics demonstrate the effect of a superimposed reinforcing influence. The status of the 4 high cases is by no means so certain. A mechanical (physicochemical) impedance may have been, but was not certainly, the cause. It is a fact, however, that in the thousands of cases which have been tested with this sugar, there is concrete evidence pointing to a renal influence on tolerance. On the other hand, all the Addisonians have very real renal impairment and, as noted, all present significantly lowered tolerances. The facts are reported as they have been found; the correct explanation of them is not so surely forthcoming.

TABLE 8.—GALACTOSE TOLERANCE. CASTRATES (25).

Tolerance dose, gm.	Number.	Deviation, per cent.	Comment.
30	4	+50	Advanced nephritics.
20	17	±0	Uncomplicated.
10	2	−50	Syphilis.
5	2	−75	Syphilis.

In the second group showing a significant complication, the evidences are simpler and more concordant. It will be remembered that thyroid failure either raised the tolerance or failed to modify its normal level.

In the present series of thyroid failure complicated by various forms of hepatic dysfunction—all carefully substantiated by a variety of objective approaches—there were 10 males and 40 females. The ages ran from 12 to 70 years, with an average of 35.7, or definitely older than the uncomplicated group. But 2% showed glycosuria, and the blood-sugar data were rigorously normal (73 mg. and 114 mg. the extreme values) with an average of 90 mg. The galactose data are given in Table 9:

TABLE 9.—GALACTOSE TOLERANCE. THYROID FAILURE AND HEPATIC DYSFUNCTION.

Tolerance.	Number or average, per cent.
Normal	2
Below normal	98
Av. deviation	−55
Group deviation	−54

Of the series, 98% showed a depressed tolerance, and the average is at a level comparing favorably with the endocrine agencies which produce the most marked depression. Here the relatively slight upward trend of the thyroid failure is more than overbalanced by the more powerful depressing influence of the liver disturbances. With the exception of the liver,[1–9] all of the non-glandular conditions tend uniformly to produce a lowering of sugar utilization. Their principal effect then would be manifest in those incretory

states usually characterized by augmented tolerances, in other words, failures of the thyroid and the pituitary glands. The few cases from these categories presenting significant complication are collected in Table 10.

TABLE 10.—INFLUENCE OF COMPLICATIONS.

Gland and function.	Complication.	Number.	Average deviation, per cent.	Group deviation, per cent.
Pituitary hypofunction	Tumor	3	+128	
	Epilepsy	3	+78	
	Central neural lesion	4	+76	
	Gall bladder	4	+61	+83
Thyroid hypofunction	Central neural lesion	3	±0	
	Syphilis	2	±0	±0

The tumor cases are included here on the implication that their presence might increase intracranial pressure, and this in turn be productive of influence on other brain tissues. Actually, no such evidence is here forthcoming, and the 6 intrasellar tumor cases in the dysfunctional group are potentially supporting with an average depression of but −31%. The other figures speak for themselves, with the exception of the 2 thyroid cases with lues. They were both advanced in years, both had chronic interstitial nephritis, and with both the syphilis had been vigorously treated with seemingly a real measure of success.

Those cases in the total series may be briefly reviewed which exhibited normal tolerances in the demonstrated presence of conditions which would be usually assumed to produce abnormality. For purposes of completeness and to emphasize intrinsic differences, the complete thyroid data are also included.

TABLE 11.—GALACTOSE TOLERANCE. ANALYSIS OF NORMAL TOLERANCE.

Gland and function.		Total.	Menopause.	Remainder.
Pituitary:	Dysfunction	11	7	Tumor, 1. Head trauma, 3.
	Hypofunction	3	2	Tumor, 1.
Thyroid:	Hyperfunction	1	1	0
	Dysfunction	25	0	Uncomp., 25.
	Hypofunction	132	28	Uncomp., 104
Ovary:	Hypofunction	7	7	0
Pancreas:	Hypofunction	4	3	Liver, 1.

As was noted earlier in the text, the postmenopausal cases introduce a minor complication with a double standard for normal performance. If, for example, 30 gm. were the true level, then all of the 40-gm. cases would show a slight increase (+33%). Equally, were 40 gm. the correct standard, the 30-gm. cases would present

a modest depression of −25%. The convention adopted of reporting both of these groups as normal makes possible the subclassification that is shown in Table 12. Further, the few remaining cases (exclusive of the thyroid series) show complications to which may be traced their abnormal normality.

To complete the survey of the postmenopausal factor, all of the pertinent data have been collected in Table 12.

TABLE 12.—GALACTOSE TOLERANCE. POSTMENOPAUSAL CASES.

Gland and function.		Positive.		Increased or diminished.	Total.
		40 gm.	30 gm.		
Pituitary:	Hyperfunction	0	0	1 Dim.	1
	Dysfunction	2	5	22 Dim.	29
	Hypofunction	2	0	12 Inc.	14
Thyroid:	Hyperfunction	0	1	3 Dim.	4
	Dysfunction	0	0	0	0
	Hypofunction	9	19	1 Inc.	29
Ovary:	Hypofunction	0	7	19 Dim.	26
Pancreas:	Hypofunction	0	3	8 Dim.	11
Adrenal:	Hypofunction	0	0	0	0
Totals		13	35	66	114

Of the total of 114 postmenopausal cases, 66 show deviations which are wholly consistent with their demonstrated glandular status, and the uncertainty of the standard can affect only the numerical expression of their deviation and that in but non-significant amount. Of the remaining 48 cases, 28 fall in the hypothyroid group where a normal tolerance is the usual finding. There remains, then, only 20 cases—2% of the series—in which the postmenopausal uncertainty could produce minor arithmetical variation. Patently, the effect is negligible. In view of the running comment throughout the body of the paper, further discussion is unncessary, and the results can be compactly summarized in tabular form.

TABLE 13.—SUMMARY OF AVERAGE DEVIATIONS.

Gland.	Hyperfunction, per cent.	Dysfunction, per cent.	Hypofunction, per cent.
Pituitary	−58	−49	+71
Thyroid	−58	−22	+ 5
Ovary	—	—	−45
Pancreas	—	—	−48
Adrenal	—	—	−62

In considering the numerical values, it must be emphasized that they are only rough indices showing direction with certainty, but amounts of deviation only as an order of magnitude. The 10-gm. stadia of the test, the inclusion of all degrees of severity of involvement within the single group from which the average deviation is reported preclude the attachment of deep significance to small percentile differences.

Adrenal failure, with pituitary and thyroid hyperfunction, constitute one group, pituitary dysfunction, diabetes and ovarian failure a second, while severally, thyroid dysfunction, thyroid failure and pituitary failure forms each an independent gradation.

The author expresses his deep appreciation both to the subjects of this investigation and, more especially, to his colleagues and associates who have contributed the vast amount of factual evidences upon which the study is based and of which the galactose testing forms but a very small part.

BIBLIOGRAPHY.

1. (*a*) Rowe, A. W.: The Metabolism of Galactose: I. The Threshold of Tolerance in Normal Adults, Arch. Int. Med., **34**, 388, 1924. (*b*) Rowe, A. W., and Chandler, J.: The Metabolism of Galactose: II. Blood Sugar Curves, Endocrinology, **8**, 803, 1924. (*c*) Rowe, A. W.: Sugar Tolerance as an Aid to Diagnosis, J. Am. Med. Assn., **89**, 1403, 1927. (*d*) Rowe, A. W., and McGuinness, M.: The Metabolism of Galactose: IV. The Effect on the Tolerance of the Level of Ovarian Activity, Am. J. Obst. and Gynec., **16**, 687, 1928. (*e*) Rowe, A. W., and McGuinness, M.: The Metabolism of Galactose: V. The Effect on the Tolerance of the Cycle of Reproduction, Ibid., **17**, 351, 1929. (*f*) Rowe, A. W., and McManus, M.: Non-diabetic Glycosurias, Am. J. Med. Sci., **179**, 761, 1930. (*g*) Rowe, A. W., and McManus, M.: The Metabolism of Galactose: IX. The Influence of Hepatic Dysfunction on Tolerance, Ibid., **181**, 777, 1931.

2. Houssay, B. A., and Biasotti, A.: Hypophysis, Carbohydrate Metabolism and Diabetes, Endocrinology, **15**, 511, 1931; Pankreasdiabetes und Hypophyse beim Hund, Pflüger's Arch. f. d. ges. Physiol., **227**, 664, 1931; and numerous other papers from Houssay and associates.

3. Barnes, B. O., and Regan, J. F.: The Relation of the Anterior Pituitary to Carbohydrate Metabolism, Endocrinology, **17**, 522, 1933.

4. Allen, F. M.: Glycosuria and Diabetes, Boston, Leonard, 1913.

5. Hofmeister, F.: Ueber Resorption und Assimilation der Nährstoffe: Fünfte Mittheilung: Ueber die Assimilationsgrenze der Zuckerarten, Arch. f. exp. Path. u. Pharmakol., **25**, 240, 1888–1889.

6. Rowe, A. W.: The Differential Diagnosis of Endocrine Disorders, Baltimore, Williams & Wilkins Company, 1932.

7. Rowe, A. W., and Lawrence, C. H.: Studies of the Endocrine Glands: IV. The Male and Female Gonads, Endocrinology, **12**, 591, 1928.

8. Falta, W., Eppinger, H., and Rüdinger, C.: Ueber den Einfluss der Schilddrüse auf den Stoffwechsel, Verhandl. d. Kong. f. inn. Med., **25**, 345, 1908.

9. Erdheim, M.: Galactose Tolerance in Latent Tetany, J. Lab. and Clin. Med., **11**, 1140, 1926.

10. Goetsch, E., Cushing, H., and Jacobson, C.: Carbohydrate Tolerance and the Posterior Lobe of the Hypophysis Cerebri: An Experimental and Clinical Study, Bull. Johns Hopkins Hosp., **22**, 165, 1911.

11. Lawrence, C. H., and Rowe, A. W.: Studies of the Endocrine Glands: V. The Adrenals, Endocrinology, **13**, 1, 1929.

12. Roe, J. H., and Schwartzman, A. S.: Galactose Tolerance of Normal and Diabetic Subjects and the Effect of Insulin Upon Galactose Metabolism, J. Biol. Chem., **96**, 717, 1932.

13. Karr, W. G., and Letonoff, T. V.: Metabolism of Galactose in Diabetes Mellitus, Am. J. Med. Sci., **185**, 596, 1933.

14. Eppinger, H., Falta, W., and Rüdinger, C.: Ueber die Wechselwirkungen der Drüsen mit innerer Sekretion, Ztschr. f. klin. Med., **66**, 1, 1908; Ibid., **67**, 380, 1909.

15. Porges, O., and Adlersberg, D.: Zum Kohlenhydratstoffwechsel der Addisonschen Krankheit, Arch. f. exp. Path. Pharmak., **172**, 433, 1933.

16. Rowe, A. W.: The Association of Hepatic Dysfunction With Thyroid Failure, Endocrinology, **17**, 1, 1933.

THE METABOLISM OF GALACTOSE.

VII. The Influence on Tolerance of Coexisting Endocrinopathies.

By Allan Winter Rowe, Ph.D.,
DIRECTOR OF RESEARCH, EVANS MEMORIAL, BOSTON, MASS.

(From the Evans Memorial, Massachusetts Memorial Hospitals.)

In a recent paper[1] dealing with the influence of individual endocrine dysfunctions on the utilization capacity of the organism for galactose, note was made of a possible disturbing effect upon the expected tolerance through a coëxistent non-endocrine condition also influencing sugar metabolism. As illustration, data were presented from a series of patients with both thyroid failure and hepatic dysfunction in which, almost without exception, the depressing influence of the liver disorder overweighed the modest augmenting tendency of the lowered incretory function. It is reasonable to assume that where two or more agencies are operating in the same organism, the resultant will be the algebraic summation of the several influences, each expressed in its degree and direction. Houssay's pioneer work,[2] supplemented by the confirmatory data from more recent studies and other sources, leaves no doubt that such a condition operates when two specific endocrine glands are in question, the depressing influence of pancreatectomy balancing the augmenting effect of ablation of the pituitary.

While the so-called pluriglandular syndrome, in the older conventional use of the term, is seemingly the rarest of occurrences, yet in a long series of individuals with endocrine involvement occasionally a case presents in which the malfunction of two ductless glands is seemingly coëxistent. Even here there may be a reasonable question if one of the two was not the primary focus and the involvement of the second no more than one feature of a general derangement which in time may influence both other incretory and non-incretory structures alike. Waiving further discussion of this still controversial topic, it remains a fact that whether the aberrant functions be coincident or sequential in their genesis, at rare intervals an individual is studied who seemingly presents such a status. A more productive source of material lies in the larger group of patients who present a technical pluriglandularity in that a dysfunctional or hypofunctional condition of surgical origin of one gland is superimposed upon a hormonal abnormality of a second. Drawing upon both types of material, it has seemed interesting to ascertain how far the predicate of opposing or reinforcing effects

can be substantiated by direct observation. The present paper deals with such a survey.

In the earlier communication already cited, the analysis of 1000 carefully studied cases gave certain criteria of the several influences on tolerance, both as to direction and roughly as to amount. Hyperfunctional and hypofunctional states are largely the antithesis of each other and require no detailed description. The term dysfunctional has been reserved in this discussion for those conditions where the gland is in a state of transition from one functional level to another or where, as in the case of hypophysis, two or more differentiated tissues constituting a single gland offer a variety of permutational possibilities. The results of the initial study may be abstracted in tabular form, dealing only with the structures which are involved in the present study.

TABLE 1.—AVERAGE DEVIATIONS OF GALACTOSE TOLERANCE.

Gland.	Hyperfunction, per cent.	Dysfunction, per cent.	Hypofunction, per cent.
Pituitary	−58	−49	+71
Thyroid	−58	−22	+ 5
Ovary	..	..	−45
Pancreas	..	..	−48

But little additional comment need be made. The differences of degree and direction are obvious. Emphasis should be laid on the fact that too great significance must not attach to the actual numerical values. These are no more than averages, drawn from groups of patients whose glandular disturbances range from mild to severe. As this same limitation obtains throughout the several groups, some slight quantitative meaning is inherent in the several magnitudes; they are to be regarded, however, as tendential rather than definitive.

The omissions in the table have already been discussed in the previous paper and elsewhere. The technique of the application of the Hofmeister[3] test, the establishment of normal criteria and other pertinent details have all been previously presented.[4]

The present series is confined to the female sex and all of the subjects had matured. The adult female tolerance level of 40 gm. applies to all of the group except those few individuals who had passed the natural climacteric. With the cases falling in this category, and following the previous convention, response to either 30 or 40 gm. is recorded as normal (±0%), and deviations above or below these levels are calculated from the mean value of 35 gm. The warrant of these conventions has been documented in the previous paper.[1]

Turning now to the present group, the cases composing it can be presented in tabular form:

TABLE 2.—COMPOSITION OF GROUP.

Pituitary.	Thyroid.	Ovary.	Pancreas.	Number.		
				Surgical.	Functional.	Total.
Dysfunction	Dysfunction	...	...	3	3	6
Hypofunction	Hypofunction	...	...	0	2	2
Hypofunction	...	Hypofunction	...	11	0	11
Dysfunction	...	Hypofunction	...	5	0	5
...	Hyperfunction	Hypofunction	...	3	0	3
...	Dysfunction	Hypofunction	...	7	0	7
...	Hypofunction	Hypofunction	...	7	0	7
Dysfunction	...	...	Hypofunction	0	4	4
...	...	Hypofunction	Hypofunction	2	0	2
			Totals . .	38	9	47

It is perhaps apposite to note that all of these patients had been hospitalized for periods of not less than a week—many of them for appreciably longer intervals—and that each had received exhaustive and detailed clinical and laboratory studies. Every effort was made to ascertain the presence of potentially disturbing complications, and the possible influence of the several individual conditions elicited will be discussed later in the text.

The surgical cases either present one or more previous subtotal thyroidectomies or an earlier bilateral ovariectomy; a few exhibited both. Those of purely functional origin are limited to pituitary-thyroid and pituitary-pancreas combinations. The latter has been reported from time to time in the more authoritative endocrine literature; the former as a possibility is apparently gathering form and substance as an entity as our knowledge of pituitary agencies is being enlarged and formalized. In 2, at least, of our 5 non-surgical thyroid-pituitary cases the association was certainly no more than a sequential one. Earlier pituitary malfunction had produced characteristic stigmata,[5] which persisted into the later adult years at the time when the individual was being studied. At this time of examination the thyroid influence determined the diagnostic pattern. With the diversity of influences, operating quantitatively and directionally, which this small group presents, it is a matter of no little difficulty to collate even the limited data of the carbohydrate metabolism within reasonable compass. Substituting the symbols +, ± and − for respectively hyperfunction, dysfunction and hypofunction, certain of the pertinent material may be collated.

The prevailing ages are high in comparison with the cross-section of the average diagnostic service which contains these several endocrine entities. As the low ages indicate, an occasional

younger person falls in one or another category, but such occurrence is rare. Seemingly the time factor for the development of the presenting conditions is a considerable one, a situation which could well have been anticipated.

TABLE 3.—AGE.

	Group.	High.	Low.	Average.
1–*a*	P ± T ±	63	36	47
b	P −, T −	56	51	54
2–*a*	P −, G −	56	18	47
b	P ±, G −	50	30	42
3–*a*	T +, G −	60	41	52
b	T ±, G −	56	26	43
c	T −, G −	54	19	40
4–*a*	Pan −, P ±	56	26	39
b	Pan −, G −	63	57	60

The blood and urine data reflect certain aspects of the sugar metabolism.

TABLE 4.—BLOOD AND URINE DATA.

	Group.	Glycosuria.		Blood sugar.		
		% +.	Amt. (av.).	High.	Low.	Av.
1–*a*	P ±, T ±	33	Traces	104	84	98
b	P −, T −	0	..	107	96	102
2–*a*	P −, G −	0	..	118*	83	96
b	P ±, G −	60	Traces	108	90	96
3–*a*	T +, G −	67	Trace	85	98	90
b	T ±, G −	0	..	111	89	101
c	T −, G −	0	..	100	68	86
4–*a*	Pan −, P ±	75	12 gm.	290	145†	212
b	Pan −, G −	100	44 gm.	230	223	227

* Emotional response.
† Insulin.

In the main, the prevailing blood-sugar levels fall within the conventional normal range and present nothing distinctive; the same is true for the uncomplicated individual endocrinopathies. A predictable exception to the above is found in the hyperglycemia of the diabetics, while the castrates with thyroid failure show a low normal level.

The agencies strongly depressing tolerance are pituitary dysfunction, thyroid hyperfunction and ovarian and pancreatic failure. The incidence and amount of glycosuria reflects these influences in the several subgroups, exception being where the powerfully augmenting influence of pituitary failure is manifest, and less strikingly in Group 3–*c*, where thyroid failure opposes the depressing effect of castration. Only among the diabetics does the sugar elimination reach significant proportions, 1 or 2 gm. or even less being the usual report from the other positive urines.

In reporting the observed galactose tolerance it should be borne in mind that the actual number of cases in any one subgroup is very small, and also that within the series wide variations occur in the degree of the incretory involvement. This, of course, is not the

case with the castrates, all of whom present a complete hypogonadism, but it applies specifically to all of the complementary functional derangements and even to those presenting the end results of subtotal thyroidectomy. For this reason, high and low values are recorded as indicating the scatter within the single class. The averages are to be regarded only so nearly representative as the small number of cases warrants. In 3 of the subgroups the tolerances were identical, but the groups were small and additional cases, in all probability, would have recorded differences.

TABLE 5.—GALACTOSE TOLERANCE.

	Group.	Deviation (%).		
		High.	Low.	Average.
1–*a*	P ±, T ±	−85	−25	−57
b	P −, T −	+71		+71
2–*a*	P −, G −	+100	±0	+20
b	P ±, G −	−75		−75
3–*a*	T +, G −	−75		−75
b	T ±, G −	−75	−25	−61
c	T −, G −	−50	−25	−40
4–*a*	Pan −, P ±	−50	−43	−48
b	Pan −, G −	−75	−50	−63

In Group 1–*a* both factors tend to depress tolerance, while in 2–*a* both exercise an opposite effect, that of the pituitary being the most powerful augmenting influence of which we have record.

In Group 2–*a* the depressing effect of castration is outweighed by the pituitary influence and a moderate increase results. With the dysfunctional pituitary, the effect is to lower tolerance, and this reinforces the like influence exercised by castration. In the three thyroid-ovary groups the average values show roughly the progress from significant reinforcement to a terminal partial compensation of ovarian depression as the hormonal activity of the first gland declines.

In the fourth group, in which the pancreas is one of the component factors, the pituitary (*a*) seemingly exercises but slight influence, the average being that earlier recorded for uncomplicated diabetes (Table 1). On the other hand, castration exercises its invariable depressing effect and that in women of fairly advanced age, certainly beyond the natural menopausal boundary.

While recognizing that any arithmetical expression with such small numbers of cases and with the variations in degree of functional involvement within the group can define no more than a trend, the consistency of the postulate may be roughly estimated by such an approach. Taking the deviation values from Table 1 for the uncomplicated influence of each entity, their algebraic summations give a calculated value for each of our present subgroups. A single exception is made in the use of −50% for the surgical hypogonad case, the figure in Table 1 including mild functional

derangements and thus lessening the average deviation from that of total failure.

TABLE 6.—CORRELATIONS.

	Group.	Number of cases.	Tolerance deviation (%).	
			Calculated.	Observed.
1–*a*	P ±, T ±	6	−71	−57
b	P −, T −	2	+76	+71
2–*a*	P −, G −	11	+21	+20
b	P ±, G −	5	−99	−75
3–*a*	T +, G −	3	−108	−75
b	T ±, G −	7	−72	−61
c	T −, G −	7	−45	−40
4–*a*	Pan −, P ±	4	−97	−48
b	Pan −, G −	2	−98	−63

Before discussing the degrees of correlation, one point must be considered. There is a definite and intrinsic arithmetical limit to the numerical expression of depression; in addition, with but one exception (−85% in Group 2–*a*), none of the subjects in the present series were tested with less than 10 gm. of sugar, thus defining a maximum deviation of −75%.

On this basis, Groups 1–*b*, 2–*a* and 3–*c* show a high, and 1–*a* and 3–*b* a satisfactory, degree of correlation. In Groups 2–*b*, 4–*b* and, most significantly, 3–*a*, the summation of the influences exhibit the limitation of the arithmetical approach with calculated values that exceed those which could possibly be reached under the convention of the testing. Even in these groups the reinforcing influence of one depressing agent upon its fellow is clearly manifest. In short, with the single exception of Group 4–*a*, in which the pancreas and pituitary participate, there is complete harmony in direction and a rough, consistent approximation in degree. In fact, the closeness of correlation in Groups 1–*b*, 2–*a* and 3–*c* must be regarded as fortuitous.

Turning for a moment to the one divergent comparison and recognizing that the predicted value of −97% is equivalent to no more than a −75% for the observed, we find that the 4 cases comprising the series showed, respectively, −25%, −43%, −50% and −75%. Conventionally these were all designated as dysfunctional states of the pituitary, but if only one (that at −25%) were adjudged to be a pituitary failure, the calculated deviation would become −70%, or in most satisfactory concordance with the observed average. While this offers a plausible explanation of the discrepancy in this group, the far-reaching effect of so minor a manipulation again emphasizes the need of considering the numbers as recorded as no more than rough indices of relative magnitudes.

In the earlier paragraphs mention was made of disturbing effects from non-endocrine agencies. The few cases in the series where such conditions obtain may be briefly reviewed.

There were 4 cases with actual or potential neural injury, including

1 postencephalitic, 2 cases with previously fractured skulls, none of whom gave positive evidences of current neural abnormality, and 1 with intrasellar tumor. This last case was a woman, aged 39, a diabetic, and was the patient showing the minimum deviation of −25% in the galactose tolerance. While, as previously noted, she was recorded as of dysfunctional pituitary status, the galactose level, aside from other considerations, would seemingly indicate a partial compensation, through pituitary failure, of the depressing pancreatic influence. A modest further support is found in the blood-sugar level of 163 mg., the lowest recorded in the non-insulinized diabetic group. Finally, her urine was free from sugar, the only case in the group. In view of the experimental results previously noted,[2] this case assumes peculiar interest. Two of the other neural cases gave tolerances consistent with their respective endocrine status; the third is discussed below.

Four cases gave evidence of some degree of hepatic dysfunction, of which 3 showed tolerances seemingly defined by the endocrine status. The remaining case may receive brief comment. The patient was a woman, aged 48, with an earlier history of encephalitis but without demonstrable residua. There was definite hepatic dysfunction; the endocrine status was a pituitary failure with surgical hypogonadism. She responded first to a test meal of 80 gm. or +100%. Her predicted tolerance would be increased, but only to a moderate degree, as the ovarian depression operates against the pituitary. The observed tolerance—uniquely high for this group—may be ascribed to the hepatic influence. While ordinarily liver disorders depress sugar tolerance, we have recorded[6] a small number of cases in which the opposite condition obtains. True, one could assume a dominant pituitary effect here, and, indeed, such may be the case. The other explanation is a possibility that warrants mention.

To complete the tale of non-endocrine factors, there were 2 psychotic and 1 psychoneurotic patient in the series, all of whom gave no evidence of a superimposed effect from this cause. The limits of variation in most of the subgroups were sufficiently elastic to absorb moderate additional effects without changing the sign of the observed deviation.

Summary. This material appears to support the postulate, that the end result of the galactose tolerance, as observed in the individual human being, reflects the algebraic summation of the several influences where more than one is operative. This emphasizes alike the need for caution in the interpretation of a single evidence and the unwisdom of establishing a diagnosis on an unsupported single end result, common to a number of causes, in terms of one of them. Seemingly, the utilization capacity for galactose in the human being is influenced by a number of agencies not demonstrably interrelated with each other and capable of independent functioning.

BIBLIOGRAPHY.

1. Rowe, A. W.: The Metabolism of Galactose: III. The Influence of Disturbed Endocrine Function, Am. J. Med. Sci., 190, 686, 1935.

2. Houssay, B. A., and Biasotti, A.: Hypophysis, Carbohydrate Metabolism and Diabetes, Endocrinology, **15**, 511, 1931; and numerous other papers from Houssay and associates.

3. Hofmeister, F.: Ueber Resorption und Assimilation der Nährstoffe. Fünfte Mittheilung: Ueber die Assimilationsgrenze der Zuckerarten, Arch. f. exp. Path. u. Pharmakol., **25**, 240, 1888–1889.

4. Rowe, A. W.: Sugar Tolerance as an Aid to Diagnosis, J. Am. Med. Assn., **89**, 1403, 1927; and numerous other papers with associates.

5. Mortimer, H., Levene, G., and Rowe, A. W.: Certain Cranial Dysplasias and Their Relation to Present Endocrinopathies, Endocrinology (in press).

6. Rowe, A. W., and McManus, M. A.: The Metabolism of Galactose: IX. The Influence of Hepatic Dysfunction on Tolerance, Am. J. Med. Sci., **181**, 777, 1931

BOOK REVIEWS AND NOTICES

NUTRITION AND DISEASE. The Interaction of Clinical and Experimental Work. By EDWARD MELLANBY, M.D., F.R.C.P., F.R.S., Late Professor of Pharmacology, University of Sheffield; Consulting Physician, Royal Infirmary, Sheffield; Secretary of Medical Research Council. Pp. 171; illustrated. London: Oliver & Boyd, 1934. Price, 8/6.

THIS short volume of 170 pages, packed with interesting experimental data and clinical observations, is a fine illustration of the interaction of Laboratory and Clinic.

The material presented represents the essence of the Croonian Lectures delivered before the Royal College of Physicians in June, 1933, and includes chapters on Rickets, Dental Structure and Disease, and a noteworthy discussion of disorders of the Thyroid Gland. The section on Nutrition and Infection, discussing particularly puerperal sepsis and septicemia, presents information of practical importance to obstetricians and surgeons.

Of especial interest is the discussion of Nutritional Influences on the Nervous System, in which the author correlates experimental work on animals with pathologic changes observed in pernicious anemia, subacute combined degeneration, disseminated sclerosis and xerophthalmia. It is stated that whereas watery extracts of liver may improve the blood picture of pernicious anemia, the protective agent against cord degeneration is a fat soluble factor, namely, vitamin A. Commercial liver extracts do not prevent nervous degeneration in dogs on a diet deficient in vitamin A. Thus Mellanby believes that whole liver plus vitamin A, used over an extended period of time, is the best therapy for pernicious anemia.

The work is generously illustrated with charts, sketches, clinical picture and microphotographs. The illustrations of nervous system lesions of nutritional deficiency origin are particularly noteworthy. The author has a pleasing style with plausible arguments and logical deduction.

This small book is a substantial contribution to the study of Nutrition and Disease. E. B.

KREBS IM LICHTE BIOLOGISCHER UND VERGLEICHEND ANATOMISCHER FORSCHUNG. By MED. DR. JOSEF LARTSCHNEIDER, LINZ A. D. DONAU. II. Band, Heft 2, Adenomkrebs Kystom Scirrhus Bindegewebe Mesenchym Sarcom Odontom Kieferkystom. Vienna: Franz Deuticke, 1935. Price, M. 7.

IN the second volume the author continues to propound his dubious conceptions of the histogenesis and biologic behavior of malignant tumors. There are, moreover, several chapters dealing with subjects having no relation to the cancer problem, such as a polemic discussion of the character of Virchow and its relation to cellular pathology, explanations concerning the causative mechanism of death in empyema, etc. A few quotations of the dogmatic assertions may best illustrate the type and scientific value of the book.

Basing his discussion of the histogenesis of adenocarcinoma mainly on the findings made by Eberth, in 1868, on multiple cystadenomas of the skin in one frog, the author asserts that they are of carcinomatous character and did not kill the frog because adenocarcinomas are of muscular

origin and represent a collagenous, glue-producing cancer tissue which is unable to attack the parakeratotic covering of the frog. These "adenocarcinomas" in the frog's skin are according to Dr. Lartschneider irritatively formed coelom cavities and vestigial nephridium formations. As undifferentiated mesenchymatous cells are first transformed into spindle-shaped muscle cells, then into myoepithelial cells, and finally into columnar epithelial cells, and, as the replacement of desquamated epithelial cells of mucous membranes is accomplished by a proliferation of the cells of the muscularis mucosa and muscularis, the gigantic hypertrophy of the muscular tissue in the stomach, intestine and bladder in the presence of desquamative processes of the epithelial lining of these organs finds thereby a ready explanation which nobody should doubt. The marked tendency of mesenchymatous tissue and preskeletal muscle tissue to become transformed into glandular tissue accounts for the occurrence of adenomas and pseudocoelomic sacs in places where normally glandular tissue is not present. Precancerous entodermal proliferations such as found in intestinal polyps may develop either into a cancer of the mucous membrane or may germinate into a mesenchymatous tissue which in turn may change into muscle tissue which after undergoing a chemical and morphologic transformation may turn into a tendineous-aponeurotic connective tissue giving rise to a scirrhous carcinoma. The muscle tissue of the tongue is disposed to adenosis and therefore predisposed to produce adenocarcinomas. The vascular muscle tissue is of cross-striated type. Similar extraordinary statements are made in regard to the cancers of the skin of the hornified type.

The author explains death caused by empyema as follows: Muscle cells germinate in the purulent matter completely independent from the organism. For the production and maintenance of these cells heat is required which is produced and taken from the organism resulting in the causation of fever. In case the empyema is too large the body is unable to supply the necessary heat. The temperature needed for the breeding of cells in the empyema becomes insufficient. The empyema turns into an iceberg which attracts the heat remaining in the body and with the loss of this heat from the organism death results. Any comment to these elucidations appears to be unnecessary. W. H.

DIET AND PHYSICAL EFFICIENCY. The Influence of Frequency of Meals Upon Physical Efficiency and Industrial Productivity. By HOWARD W. HAGGARD, M.D. and LEON A. GREENBERG, PH.D., of the Department of Applied Physiology in Yale University. Pp. 180; 31 illustrations and 35 tables. New Haven: Yale University Press, 1935. Price, $3.00.

THE authors studied the influence of the frequency of meals upon physical efficiency and industrial productivity. They state that the quantity and quality of food have received a great deal of attention in recent years, but that the distribution of diet in time has not received the attention it deserves. They utilized the respiratory quotient as an index of muscular efficiency and concluded that the practice common in this country of eating the day's supply of food in three installments does not permit of the greatest efficiency of which the individual is capable. They find that, for the working man and woman as well as for the active growing child, five meals a day yield the maximum efficiency, although these five meals need contain no more calories than the usual three meals. Their conclusions were that on the same amount of food the industrial output of factory operatives may be as much as 10% greater under one mealtime arrangement than under another. E. W.

SOME THOUGHTS OF A DOCTOR. By FREDERICK PARKES WEBER, M.A., M.D., F.R.C.P., F.S.A. With a Preface by SIR W. LANGDON BROWN, M.A., M.D., F.R.C.P., Regius Professor of Physic in the University of Cambridge. Pp. 183. London: H. K. Lewis & Co., Ltd., 1935. Price, 6s.

MANY of the brief essays brought together here appeared in German translation several years ago under the more expressive title, *Gedanken eines Arztes über Seele, Natur und Gott.* Even this cosmic handle fails to define satisfactorily a collection of essays in which are considered eugenics, the psychiatrists, longevity, medical teleology, the blood as a group of organs, suicide and euthanasia, therapeutic fasting and low diet, cell memory, the gambling spirit, war atrocities and myths, among other more and less metaphysical subjects. The essays are replete with the individuality, wit, and intellectual vigor hitherto associated with Dr. Weber's literary work, and it is to be hoped that the vacuous title of the book may neither ensnare the ingenuous, nor mislead the cultured medical man whom it will please most.

W. McD., 2D

FIFTY YEARS A SURGEON. By ROBERT T. MORRIS, M.D. Pp. 347. New York: E. P. Dutton & Co., Inc., 1935. Price, $3.50.

IN this book a distinguished American surgeon looks back over a fruitful period in the development of surgical technique, and reviews with disarming candor his own and others' contributions, salting the review with spirited reflections along the way. It is a two-fisted tale, not lacking in drama for the layman, which will provide the older medical man with the sometimes dubious pleasures of recollection, and the younger with a stimulating perspective on his craft. Such records as this serve notably both the cause of medical history and the better understanding between layman and physician.

W. McD., 2D.

CHILD PSYCHIATRY. By LEO KANNER, M.D., Associate Professor of Psychiatry, The Johns Hopkins University, Baltimore. With Prefaces by ADOLF MEYER, M.D., LL.D., Henry Phipps Professor of Psychiatry, The Johns Hopkins University, and EDWARD A. PARK, M.D., Prof. of Pediatrics, The Johns Hopkins University. Pp. 527. Springfield, Ill.: Charles C Thomas, 1935. Price, $6.00.

THE author in his introduction makes the following statement: "The present volume, which is offered as the first textbook of child psychiatry in the English language, is offered as an attempt to cover the entire field of children's personality disorders on a broad, objective, unbiased and practical basis."

With excellent prefaces by Dr. Edward A. Park and Dr. Adolf Meyer, the book starts off with a consideration of the various schools of psychiatric thought and follows this with an excellent chapter on the principles of child psychology, giving the reader a good foundation for the chapters which follow on the specific problems to be encountered in the difficult child.

The author's vast experience at the Harriet Lane Home of the Johns Hopkins Hospital and at the Henry Phipps Psychiatric Institute is clearly brought out in his able discussion of every conceivable mental disorder of childhood. He is obviously a great admirer of Dr. Meyer, and the latter's common sense philosophy is everywhere present in the book. The psychoanalytical school is given credit where credit is due, but it is obvious that the author does not consider these methods by and large applicable to the common disorders of childhood.

Principles rather than specific therapeutic procedures are given in the discussion of the treatment of the various disorders. As Dr. Meyer once said, "A child guidance clinic must not be merely a center for the distribution of tricks." Each individual case must be analyzed from every angle. When the physical condition, heredity and environment have all been carefully studied the course of treatment will often suggest itself.

This is a book which should be of interest not only to physicians but to laymen interested in the problem child as well. It is extremely well written, offers a wealth of clinical material, and offers something which has long been greatly needed.

A. McG.

TUMORS OF THE URINARY BLADDER. By EDWIN BEER, M.D., F.A.C.S., Visiting Surgeon, Mount Sinai Hospital; Consulting Surgeon, Bellevue Hospital, New York City. Pp. 166; 52 illustrations; 8 in colors. Baltimore: William Wood & Co., Price, $3.50.

THIS brief but comprehensive monograph is of importance because of the author's well known contributions to the therapy of these tumors and his sustained interest in the subject for the past twenty-five years. The book deals principally with the epithelial growths because, the author points out, other types of bladder neoplasms are rarities. The author's concise classification of the epithelial tumors of the bladder forms the basis for his discussion of the symptomatology, pathology and treatment. Typical benign and malignant lesions as they appear through the cystoscope are well illustrated. The cystoscopic pictures of conditions resembling tumors are fully discussed. In the Chapter on the Consideration of Treatment of Bladder Tumors the author points out the fallacy of dogmatism in this field and lists the various procedures which he has found of value. He discusses the indications for these different methods in the management of the various types of neoplasms encountered. The author also discusses other methods used by various groups, although few direct references are made to the extensive bibliography.

J. McC.

NEW BOOKS.

Puerperal Gynecology. By J. L. BUBIS, M.D., F.A.C.S., Consultant in Obstetrics, Gynecologist, Mt. Sinai Hospital, Cleveland; Member of Central Association of Obstetricians and Gynecologists. Foreword by P. BROOKE BLAND, M.D., Professor of Obstetrics, Jefferson Medical College, Philadelphia. Pp. 199; 81 illustrations and 22 tables. Baltimore: William Wood & Co., 1935. Price, $3.50.

Diseases of the Liver, Gall Bladder, Ducts and Pancreas. Their Diagnosis and Treatment. By SAMUEL WEISS, M.D., F.A.C.P., Clinical Professor of Gastro-enterology, New York Polyclinic Medical School and Hospital; Attending Gastro-enterologist, Jewish Memorial and Beth David Hospitals, New York, etc. Chapter on Surgery by J. PRESCOTT GRANT, M.D., F.A.C.S., M.R.C.S., Professor of Surgery, New York Polyclinic Medical School and Hospital; Attending Surgeon, City Hospital; Director of Surgery, Midtown Hospital. Chapter on Roentgenology by A. JUDSON QUIMBY, M.D., F.A.C.R., Professor of Roentgenology, New York Polyclinic Medical School and Hospital; Visiting Roentgenologist, Broad Street Hospital. Pp. 1099; 358 illustrations, 6 color plates and 21 tables. New York: Paul B. Hoeber, Inc., 1935. Price, $10.00.

Tumors of the Urinary Bladder. By EDWIN BEER, M.D., F.A.C.S., Visiting Surgeon, Mount Sinai Hospital; Consulting Surgeon, Bellevue Hospital, New York City. Pp. 166; 52 illustrations, 8 in colors. Baltimore: William Wood & Co., 1935. Price, $3.50. (Review, p. 712.)

La Maladie des Pêcheurs D'Éponges Nus. By SKEVOS ZERVOS. Pp. 29; illustrated. Paris: Librairie J.-B. Baillière et Fils, n.d. (No price given.)

The Carotid Sinus and the Cerebral Circulation. An Anatomical, Experimental, and Clinical Investigation. Acta Psychiatrica et Neurologica, Suppl. VI. By ERIK LUND ASK-UPMARK, Sweden. From the Departments of Neuropathology, Neurosurgery and Anatomy, Harvard Medical School, Boston. Pp. 374; 74 illustrations and 22 tables. Copenhagen: Levin & Munksgaard, 1935. (Price not given.)

Infections of the Urinary Tract. By T. E. HAMMOND, F.R.C.S., Surgeon, The Royal Infirmary, Cardiff; Consulting Urologist, The Welsh National Memorial Association. Pp. 250; 3 illustrations and 3 charts. London: H. K. Lewis & Co., Ltd., 1935. Price, 10/6.

Disorders of the Blood. Diagnosis, Pathology, Treatment and Technique. By LIONEL E. H. WHITBY, C.V.O., M.C., M.A., M.D. (CANTAB.), F.R.C.P. (LOND.), Assistant Pathologist, The Bland-Sutton Institute of Pathology, The Middlesex Hospital, and Pathologist, The Children's Hospital, Hampstead, and C. J. C. BRITTON, M.D. (NEW ZEALAND), Assistant Pathologist, The Christchurch Hospital, New Zealand; Late Post Graduate New Zealand Scholar, The Middlesex Hospital, and Assistant Pathologist, The Bland-Sutton Institute of Pathology, The Middlesex Hospital. Pp. 543; 53 illustrations and 12 plates (8 in colors). Philadelphia: P. Blakiston's Son & Co., Inc., 1935. Price, $7.00.

Agents of Disease and Host Resistance. Including The Principles of Immunology, Bacteriology, Mycology, Protozoölogy, Parasitology and Virus Diseases. By FREDERICK P. GAY, in association with 19 others, all of whom, except 4, are past or present members of the Department of Bacteriology, College of Physicians and Surgeons, Columbia University, New York City. Pp. 1581; 212 illustrations, 6 colored plates, 125 tables and 61 diagrams. Springfield, Ill.: Charles C Thomas, 1935. Price, $10.00.

Anemias y Alimentación. El Principo Antianémico del Hígado y Los Factores Cualitativos de Los Alimentos (Vitaminas, Amenoácidos, Hierro y Cobre) Tesis Doctoral Premiada Por la Academia Nacional de Medicina in 1935. Prólogo de Gregorio Marañón. By JOSÉ SÁNCHEZ RODRÍQUEZ. Pp. 165; 22 illustrations. Madrid: Ediciones Del Arbol, 1935. (Price not given.)

Die Werke des Hippokrates. Herausgegeben von DR. MED. RICHARD KAPFERER unter Mitwirkung von PROF. DR. GEORG STRICKER, Würzburg. Book 11 (Price, Rm. 8. Pp.103): Die epidemischen Krankheiten (Die Volkskrankheiten) The Epidemic Diseases (Diseases of the People). Parts 1–3. Book 12 (Price, Rm. 9.50; pp. 135.): Die epidemischen Krankheiten (Die Volkskrankheiten). Parts 4–7. Stuttgart: Hippokrates-Verlag G.M.B.H., 1934. (To be published in 25 parts costing ca. Rm. 100, card binding.)

Food and Beverage Analyses. By MILTON ARLANDEN BRIDGES, B.S., M.D., F.A.C.P., Director of Medicine, Department of Correction Hospitals, New York; Consulting Physician, Seaview Hospital, Staten Island; Assistant Clinical Professor of Medicine and Lecturer in Therapeutics, New York Post-Graduate Medical School, Columbia University, etc. Pp. 246. Philadelphia: Lea & Febiger, 1935. Price, $3.50.

NEW EDITIONS.

Diseases of the Nervous System. A Text-book of Neurology and Psychiatry. By SMITH ELY JELLIFFE, M.D., PH.D., Formerly Professor of Psychiatry, Fordham University, and Adjunct Professor of Diseases of the Mind and Nervous System, New York Post-Graduate Medical School and Hospital, and WILLIAM A. WHITE, M.D., Superintendent of St. Elizabeth's Hospital, Washington, D. C.; Professor of Psychiatry, George Washington University, etc. Pp. 1175; 497 illustrations and 13 plates. Sixth edition, thoroughly revised. Philadelphia: Lea & Febiger, 1935. Price, $9.50.

A Text-book of Fractures and Dislocations. Covering Their Pathology, Diagnosis and Treatment. By KELLOGG SPEED, S.B., M.D., F.A.C.S., Professor of Clinical Surgery, Rush Medical College of the University of Chicago; Attending Surgeon, Presbyterian Hospital, etc. Pp. 1000; 1042 illustrations. Third edition, thoroughly revised. Philadelphia: Lea & Febiger, 1935. Price, $11.00.

Diseases of the Thyroid Gland. By ARTHUR E. HERTZLER, M.D., Chief Surgeon, Halstead Hospital; Professor of Surgery, University of Kansas. With a Chapter on Hospital Management of Goiter Patients, by VICTOR E. CHESKY, M.D., Chief Resident Surgeon, Halstead Hospital. Pp. 348; 181 illustrations. Third edition, entirely rewritten. St. Louis: The C. V. Mosby Company, 1935. Price, $7.50.

Human Pathology. A Textbook. By HOWARD T. KARSNER, M.D., Professor of Pathology, Western Reserve University, Cleveland. With an Introduction by SIMON FLEXNER, M.D. Pp. 1013; 433 illustrations, 18 in color. Fourth edition, revised. Philadelphia: J. B. Lippincott Company, 1935. Price, $10.00.

A Textbook of Laboratory Diagnosis. With Clinical Applications for Practitioners and Students. By EDWIN E. OSGOOD, M.A., M.D., Assistant Professor of Medicine and Biochemistry, Director of Laboratories, University of Oregon, School of Medicine, Portland. Pp. 585; 27 illustrations and 10 colored plates. Second edition. Philadelphia: P. Blakiston's Son & Co., Inc., 1935. Price, $6.00.

Clinical Diagnosis by Laboratory Methods. A Working Manual of Clinical Pathology. By JAMES CAMPBELL TODD, PH.B., M.D., Late Professor of Clinical Pathology, University of Colorado, School of Medicine, and ARTHUR HAWLEY SANFORD, A.M., M.D., Professor of Clinical Pathology, University of Minnesota (The Mayo Foundation); Head of Section on Clinical Laboratories, The Mayo Clinic. Pp. 792; 370 illustrations, 29 in colors. Eighth edition, thoroughly revised. Philadelphia: W. B. Saunders Company, 1935. Price, $6.00.

A Textbook of General Bacteriology. By EDWIN O. JORDAN, PH.D., Professor of Bacteriology in the University of Chicago and in Rush Medical College. Pp. 825; 202 illustrations. Eleventh edition, entirely reset. Philadelphia: W. B. Saunders Company, 1935. Price, $6.00.

PROGRESS
OF
MEDICAL SCIENCE

THERAPEUTICS

UNDER THE CHARGE OF

CARY EGGLESTON, M.D.,
ASSISTANT PROFESSOR OF CLINICAL MEDICINE, CORNELL UNIVERSITY MEDICAL COLLEGE, NEW YORK CITY,

AND

SOMA WEISS, M.D.,
ASSOCIATE PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL, BOSTON, MASS.

THE USE OF CARBON TETRACHLORID, TETRACHLORETHYLENE, HEXYLRESORCINOL AND RELATED COMPOUNDS IN INTESTINAL PARASITIC INFESTATIONS.

DURING the past decade significant progress has been made in the chemotherapy of intestinal infestations. New compounds have been introduced and some of the older remedies, such as chenopodium and aspidium, have been reinvestigated. In spite of extensive clinical trials, an evaluation of the relative clinical merits of these substances or combinations of these substances is difficult. The purpose of this review is not so much to enter into the controversial topic of the relative merits of anthelmintics as to summarize the pharmacologic and therapeutic properties of these newly introduced substances. The clinical aspect of anthelmintics has been discussed recently by Brown.[1]

Carbon Tetrachlorid. In 1921, Hall[2,3] tested the efficacy of carbon tetrachlorid in dogs, horses and swine, with particular reference to the effect of the drug on hookworms. The use of carbon tetrachlorid as an anthelmintic was suggested to him by the fact that chloroform has been applied alone and in mixtures for the removal of hookworms. In animals carbon tetrachlorid was found by Hall to be only slightly less effective than chenopodium. In view of the fact that carbon tetrachlorid was used about a half century ago as an anodyne and anesthetic, Hall took 3 cc. of the drug in hard capsules. No untoward effect was noted. He therefore suggested its use in man for removal of hookworms and ascarides. He also pointed out that carbon tetrachlorid is a chemically pure drug with definite chemical composition and thus possesses an advantage over chenopodium, which is a mixture of a number of compounds in variable proportions. Following his report this drug was used extensively. The average dose administered for adults is 3 cc., which is usually added to 30 gm. of magnesium

sulphate dissolved in half a glassful of water. The mixture is usually shaken, and swallowed in a postabsorptive state in the morning. No breakfast is eaten until the purge has acted. Following the action of the purge a warm soapsuds enema is given, and the stools are searched for worms.[1] Extensive experience with the drug, however, indicated that toxic reactions occur. Thus Lambert,[4] reporting his 10 years of experience in the treatment of 286,486 persons with various drugs, has observed 6 deaths from carbon tetrachlorid and 1 death from oil of chenopodium. He gained the impression that patients with a large number of ascarides are more sensitive to toxic reactions. Racial factors apparently also play a rôle, as all severe toxic reactions developed among East Indians. Milder manifestations of the drug were dizziness and sleepiness. "Nurses say that after treatment is given in a native village there is a strange unusual silence for the remainder of the day." Headaches, nausea and vomiting develop frequently. Jaundice and bloody stools may appear. The nature and the treatment of the intoxication have been studied extensively by Lamson, Minot and their associates.[5,6,7,8] They have demonstrated that the important underlying lesion is central necrosis of the liver. They pointed out that carbon tetrachlorid is extremely toxic, both for chronic alcoholic addicts and for those who drink alcohol immediately after treatment. The relation of alcohol to carbon tetrachlorid poisoning was also demonstrated in animals. Irritation or mechanical obstruction of the intestines by ascarides predisposed to poisoning. Migration and obstruction by the ascarides may follow the administration of carbon tetrachlorid; hence for removal of hookworms it is advisable to administer chenopodium before carbon tetrachlorid is given. Another predisposing factor was undigested food in the intestinal tract. Finally, these authors produced experimental evidence indicating that in the clinical symptomatology calcium deficiency plays an important rôle. In support of this factor they mention that children who are undernourished are particularly susceptible to carbon tetrachlorid. When both the calcium ion and the fibrinogen content of the blood are low, intestinal bleeding may be demonstrable. For the prevention of intoxication they recommend: (*a*) avoiding the administration of carbon tetrachlorid to patients with ascariasis without preliminary treatment for roundworms; (*b*) refusing treatment to alcoholic addicts; (*c*) having the patient avoid alcohol and food shortly before and after carbon tetrachlorid administration; and (*d*) insuring an adequate calcium reserve in all persons treated.

Because of these unpleasant and toxic reactions, attempts have been made to find a more suitable preparation. The early work in this field was carried out in the Zoölogical Division of the United States Bureau of Animal Industry.

Tetrachlorethylene. Hall and his associates have found that among the substances related to carbon tetrachlorid, such as ethylene dichlorid ($C_2C_4Cl_2$), carbon trichlorid (C_2Cl_6) and tetrachlorethylene (C_2Cl_4), only the latter held therapeutic promise. They found that in experimental animals tetrachlorethylene was as effective as carbon tetrachlorid for hookworms and ascarides. In the first publication Hall and Schillinger[9] believed that the safety of and lesions induced by tetrachlorethylene are about the same as those observed following the use of carbon tetra-

chlorid. Lamson, Robbins and Ward[10] undertook the investigation of tetrachlorethylene and they observed that this substance is less toxic than carbon tetrachlorid and that it produces entirely different reactions. Tetrachlorethylene is absorbed little if at all from the intestinal tract of dogs in the absence of fat. With massive doses, particularly if fat is present in the bowels, absorption may take place, resulting in intoxication and even death. The manifestations of intoxication, however, are those of a hypnotic and not those secondary to liver damage. Experiments actually failed to reveal necrosis of the liver or lesions of the kidneys. These authors suggested that "the chances of its being toxic in human beings are very slight," and they concluded that from a pharmacologic point of view tetrachlorethylene is superior to carbon tetrachlorid and chloroform for anthelmintic uses. No extreme dietary preparations are necessary. Lamson also predicted that it could be used in the treatment of hookworm disease with far greater safety than either oil of chenopodium or carbon tetrachlorid. Experienced gained by workers in the field confirmed this contention. In certain patients dizziness and giddiness may occur following the usual adult dose of 3 to 4 cc.[11] In his extensive experience Lambert[4] observed no fatalities or severe intoxication. He states, however, that the exhilarating effect is more pronounced than that of carbon tetrachlorid, though some of the bizarre manifestations among natives of the tropics are due to post-treatment hysteria rather than to the drug. It is advisable to refrain from taking fat or alcohol during the treatment. It has been estimated that as high as 77 to 97% of the hookworms were removed after a single treatment with tetrachlorethylene.[12]

Hexylresorcinol and Related Compounds. These substances have been introduced in an attempt to find a safe and effective ascaricide, in view of the fact that both santonin and oil of chenopodium may cause severe intoxication if not properly eliminated. The effective elimination of ascarides is an important problem, not only *per se*, but also in connection with hookworm campaigns. It has been found that both carbon tetrachlorid and tetrachlorethylene cause migration of the ascaris, which may result at times in fatal obstruction of the gut and air passages. The ascaris should therefore be removed before applying these drugs for hookworm eradication.

Lamson, Brown, Robbins and Ward[13] have found that hexylresorcinol fulfills the requirements for the safe eradication of ascaris infestation. It is active on ascarides *in vitro*, killing them without initial stimulation, and is relatively non-toxic. They have treated 1500 human cases with crystallin hexylresorcinol without any symptoms of consequence and with no instance of ascaris migration, and they have succeeded in removing a high percentage of both ascarides and hookworms, as well as numbers of trichuris. The drug was administered in hard gelatin capsules. Doses of 1 gm. were given to patients of 12 years or over, 0.6 to 0.8 gm. to those from 6 to 12 years, and doses of 0.4 gm. to very young children. In adults, doses below 0.5 gm. were less effective. The efficacy of hexylresorcinol was found to be greatly reduced if food was taken shortly before or after treatment. It was therefore found best to institute treatment in the morning before breakfast, allowing no food for 4 or 5 hours afterward. Full therapeutic doses removed between 90 and 100% of ascaris and hookworms in controlled

cases, so that administration of larger doses seemed unnecessary. In the group of field treatments reported by these authors an average reduction of 90% of ascarides, 80% of hookworms and 55% of trichuris was obtained. A few patients complained of slight gastric irritation and an occasional patient vomited. This was probably due to the irritant action of hexylresorcinol on the gastric mucosa, caused by the interaction of this substance in concentrated form with the protein of the superficial epithelium. On account of the insolubility of hexylresorcinol, this reaction of the mucous membrane is entirely superficial.

Brown[1] claims that tetrachlorethylene is more effective than hexylresorcinol in the removal of hookworms, and therefore is to be preferred for mass treatment. In children and in debilitated and pregnant persons hexylresorcinol is useful. Molloy[14] has used hexylresorcinol in 1784 treatments of hookworm and other intestinal helminth infestations. With the exception of slight gastric irritation, no toxic symptoms were observed. On account of the action of hexylresorcinol on gelatin, he administered the drug in sugar-coated pills rather than in gelatin capsules. Full therapeutic doses of 1 gm. removed from 65 to 72% of hookworms under field conditions. He claimed that in the treatment of ascaris infections the drug is probably without an equal. From 93 to 98% of the ascarides harbored by the individuals treated were expelled by a single dose. In the treatment of whipworm infestations, on the other hand, the drug appears to be less effective than was indicated by other workers. Even so, it was found to be the most effective drug available against this parasite. The administration of a purge 2 hours after the drug lessens its anthelmintic effect. On account of its delayed action, phenolphthalein may be administered simultaneously with hexylresorcinol without lessening its efficiency against hookworms and ascarides. If saline purgatives are employed, they should preferably not be administered until the following morning. In the treatment of hookworm disease a single dose of hexylresorcinol lessens the worm burden to the extent that the patient is relieved of most of his symptoms. It does not, however, entirely eliminate the danger to others, since the majority of individuals treated still harbor a sufficiently large number of worms to be considered "carriers."

Recently Lamson and his associates reported further anthelmintic studies on alkyl-hydroxybenzenes.[15,16,17,18] A number of alkyl-polyhydroxybenzenes have been studied for their anthelmintic action *in vitro*. Marked ascaricidal properties appeared first in the amylresorcinol and reached a maximum in hexylresorcinol. With the majority of alkylphenols the active substance will be found to occur in a solution range of from 1 to 1000 to 1 to 35,000. The melting point of the active substances is usually below 80° C.; compounds with higher melting points cannot properly come in contact with the worm and are usually ineffective.

The pharmacologic properties of hexylresorcinol have also been reinvestigated and compared with those of other substances. Its absorption and excretion have been studied quantitatively. It is of interest that no consistent lesion has been found except the local irritant effect on the gastro-intestinal tract. Hexylresorcinol was found again to be an extremely effective ascaricide, doses of 0.1 gm. per year of age up to adult doses of 1 gm. removing between 90 and 100% of

the parasites. It is less effective against hookworms, although between 70 and 80% of these parasites can be removed by a single dose. Except for its local irritant properties which cause some temporary, superficial irritation of the stomach and intestine, an effect which is unnoticed by the majority of individuals, hexylresorcinol may be considered from the experiments presented as a non-toxic substance. No case of intoxication has been reported, even after its use in many thousands of individuals.

From the studies of many polyhydroxybenzenes, Lamson and his associates feel that a certain degree of local irritant action must be present in order to allow anthelmintic activity. Anthelmintic activity is not, however, directly proportional to local irritant action. Thus the lower members of these 4-n-alkyl-resorcinols are even more irritating than hexylresorcinol, but they are not such active anthelmintics.

In spite of the fact that it was thought by these workers that the ascaricidal properties were related to the presence of the hydroxyl groups of the benzenes, the dihydroxybenzenes were not found strikingly different in their ascaricidal action from the monohydroxybenzenes. The ascaricidal properties of phenols and resorcinols are increased by the introduction of alkyl radicals. These properties become more marked as the alkyl chain is lengthened, reaching a maximum which differs in different series, and falls off rapidly in the higher members. No significant difference was found between ortho- and para-alkylphenols. The effect of other types of alterations in the structure of alkyl-hydroxybenzenes on the pharmacologic properties of the drug is discussed.

Among the substances studied there are several which theoretically should be as good human ascaricides as hexylresorcinol. There is also a possibility that some of these substances will be found of especial value in other helminth infestations, such as uncinariasis or trichuriasis. Lamson suggests that the efficacy of these substances should be tested in man.

SOMA WEISS.

REFERENCES.

1. Brown, H. W.: Intestinal Parasitic Worms in the United States. Their Diagnosis and Treatment, J. Am. Med. Assn., **103**, 651, 1934.

2. Hall, M. C.: Carbon Tetrachlorid for the Removal of Parasitic Worms, Especially Hookworm, J. Agric. Res., **21**, 157, 1921.

3. Hall, M. C.: Use of Carbon Tetrachloride for Removal of Hookworms, J. Am. Med. Assn., **77**, 1641, 1921.

4. Lambert, S. M.: Hookworm Disease in the So. Pacific; Ten Years of Tetrachlorides, J. Am. Med. Assn., **100**, 247, 1933.

5. Minot, A. S., and Cutler, J. T.: Guanidine Retention and Calcium Reserve as Antagonistic Factors in Carbon Tetrachloride and Chloroform Poisoning, J. Clin. Invest., **6**, 369, 1928.

6. Minot, A. S.: Mechanism of Hypoglycemia Produced by Guanidine and Carbontetrachloride Poisoning and Its Relief by Calcium Medication, J. Pharm. and Exp. Therap., **43**, 295, 1931.

7. Lamson, P. D., Gardner, G. H., Gustafson, R. K., Maire, E. D., McLean, A. J., and Wells, H. S.: Pharmacology and Toxicology of Carbon Tetrachloride, Ibid., **22**, 215, 1923.

8. Lamson, P. D., Minot, A. S., and Robbins, B. H.: Prevention and Treatment of Carbon Tetrachloride Intoxication, J. Am. Med. Assn., **90**, 345, 1928.

9. Hall, M. C., and Schillinger, J. E.: Tetrachlorethylene, New Anthelmintic, Am. J. Trop. Med., **5**, 229, 1925.

10. Lamson, P. D., Robbins, B. H., and Ward, C. B.: Pharmacology and Toxicology of Tetrachlorethylene, Am. J. Hyg., **9**, 430, 1929.
11. Maplestone, P. A., and Mukirji, A. K.: Carbon Tetrachlorethylene in Treatment of Hookworm Infection, Indian Med. Gaz., **68**, 617, 1933.
12. Kendrick, J. F.: Treatment of Hookworm Disease with Tetrachlorethylene, Am. J. Trop. Med., **9**, 483, 1929.
13. Lamson, P. D., Brown, H. W., Robbins, B. H., and Ward, C. B.: Field Treatments of Ascariasis, Ancylostomiasis, and Trichuriasis with Hexylresorcinol, Am. J. Hyg., **13**, 803, 1931.
14. Molloy, D. M.: Treatment of Hookworm and Other Intestinal Helminth Infections with Hexylresorcinol Under Field Conditions in Central America; Preliminary Report, South. Med. J., **26**, 575, 1933.
15. Lamson, P. D., Brown, H. W., and Ward, C. B.: Anthelmintic Studies on Alkylhydroxybenzenes; Alkylpolyhydroxybenzenes, J. Pharm. and Exp. Therap., **53**, 198, 1935.
16. Lamson, P. D., Brown, H. W., Stoughton, R. W., Harwood, P. D., Baltzly, R., and Bass, A.: Anthelmintic Studies on Alkylhydroxybenzenes; Ortho- and Para-n-Alkylphenols, Ibid., **53**, 218, 1935.
17. Lamson, P. D., and Brown, H. W.: Anthelmintic Studies on Alkylhydroxybenzenes; 6-n-alkyl-meta-cresols, Ibid., p. 227.
18. Lamson, P. D., Brown, H. W., Stoughton, R. W., Harwood, P. D., Baltzly, R., and Bass, A.: Anthelmintic Studies on Alkylhydroxybenzenes; Isomerism in Polyalkylphenols, Ibid., p. 234; Anthelmintic Studies on Alkylhydroxybenzenes; Phenols with Other Than Normal Alkyl Side Chains, Ibid., p. 239.

RADIOLOGY

UNDER THE CHARGE OF
ALBERT MILLER, M.D.,
AND
CHARLES G. SUTHERLAND, M.D.,
CONSULTING PHYSICIANS, SECTION ON ROENTGENOLOGY, MAYO CLINIC, ROCHESTER, MINN.

Mediastinal Tumors. The management of intrathoracic disease is peculiarly the responsibility of the roentgenologist, in the opinion of Evans and Witwer,[2] for his is the method of accurate detection, differential diagnosis, indication and guide in therapy, and in certain cases his may be the healing agent necessary for the optimum result. This applies particularly to intrathoracic and more especially to mediastinal neoplasms, conditions which were rarely recognized in the pre-Roentgen period and, if recognized, could not be successfully treated by methods known at that time.

Mediastinal neoplasms of all types represented less than 1% of all the neoplasms coming under their observation over a 12-year period.

Primary tumors may originate in the lymph nodes, connective tissues, thymus or thyroid gland, and in the bloodvessels of the mediastinum. In the benign group they observed: (1) Cysts (echinococcus, dermoid, etc.); (2) ganglionic neuroma; (3) fibroma; (4) chondroma; (5) lipoma; (6) aneurysm. Pathologists vary in opinion as to the histogenic nature of many of the malignant neoplasms, but, for practical purposes, they have found a satisfactory grouping to be: (1) Lymphoma (lymphosarcoma, pseudoleukemia, aleukemic leukemia, malignant granuloma,

Hodgkin's disease and thymoma); (2) sarcoma, as a rule originating from areolar connective tissue (fibrosarcoma, spindle-cell sarcoma and alveolar cell sarcoma); (3) carcinoma of thymic and thyroid origin; (4) teratoma. The essential clinical features are well known, but they particularly mention some unusual clinical features as they enter into the technique of Roentgen therapy. Very large tumors, in addition to the symptoms of respiratory embarrassment, may produce marked edema of the neck and face. Since heavy radiation treatment may increase edema and respiratory difficulty, it sometimes appears advisable to resort to the fractional method of treatment with smaller doses in cases in which the indications for such a procedure exist. Hemorrhage is a relatively rare but important complication in tumors primary in the mediastinum.

Roentgen examination should include fluoroscopic and roentgenographic examination, in the latter a study in the lateral position is most important. In addition to the information regarding the size, shape, configuration and location of tumors, secondary changes may be demonstrated which are the effect of pressure changes on surrounding structures. Outstanding among these are atelectasis of all or part of one or more lobes, and pleural effusion, the latter is not necessarily an indication of pleural metastases, it can be the result of pressure.

In their experience, shadow changes produced by some of the mediastinal tumors are not always constant and expansile pulsation is not always a safe index of an aneurysm in differential diagnosis. Visualization of the esophagus with the aid of barium, to detect encroachment upon its lumen, the intratracheal installation of lipiodol and the induction of pneumothorax to better define the tumor are aids in diagnosis. For the past 10 years an increasing effort has been made to utilize the variation in the radiosensitivity of mediastinal tumors as a guide in their differential classification. The largest dose over the tumor which can be tolerated without injury to the normal tissue (as a rule, 110 to 130% skin unit dose) is given, the variation in response of tumors is then estimated and used as an index. From the response to radiation, certain conclusions may be formed concerning the morphologic nature of the tumors irradiated. Tumors arising from the lymphocytic cell element, such as lymphosarcomas, thymomas, pseudoleukemias and lymphatic leukemias, will entirely disappear within from 4 to 10 days following the administration of a therapeutic test dose. Tumors originating from the reticulo-endothelial cells of the mediastinal lymph glands and the thymus, such as Hodgkin's disease, Sternberg type of hyperplastic tuberculosis, and endothelioma, respond more slowly, being reduced within 10 days following the administration of a therapeutic test dose to one-half their original size, and disappear entirely in about 6 weeks or longer following the treatment. Primary mediastinal tumors having their origin from the areolar tissue (such as fibrosarcoma, large round cell sarcoma, carcinoma of the thymus and thyroid glands and teratomas) show some reduction in size following exposure, but rarely disappear at the end of 6 weeks. Benign tumors of the mediastinum (lipoma, chondroma, fibroma, neuroma, dermoid) or pseudo tumors (aneurysm, mediastinal abscess, mediastinal effusion) with the exception of fibroma, which responds very slowly, are not influenced by radiation.

Extrapulmonary Tumors of the Thorax. Pierce[4] divides these into: (1) Tumors of the thoracic wall proper, which include lipoma, fibroma, myxoma, chondroma, osteochondroma and angioma in the benign group and chondrosarcoma, osteochondrosarcoma, osteogenic sarcoma of the ribs, "giant sarcoma," myxo-angio-endothelioma in the malignant group. Metastatic malignant neoplasms may involve the thoracic wall. Ganglioneuroma and neurofibroma (neurinoma) occur rarely in the thorax, the former will appear predominantly in the posterior or paravertebral gutter or the mediastinum, the latter most commonly is associated with the intercostal nerves. The neoplasm tends to be either sessile or nodular in the thoracic parieties or globular when found in the posterior gutter or mediastinum.

Tumors of the pleura of extrinsic origin include chiefly metastatic malignancy, echinococcus cyst, tuberculoma and fibrinoma, those of intrinsic origin, endotheliomas and the connective tissue tumors such as chondromas of the phrenic pleura, are rare. Lesions which properly do not arise from the thoracic wall or pleura, but which may present Roentgen changes by pressure or invasion in the wall or pleura are chiefly aneurysms of the innominate artery, new growths from embryonal rests (teratoma) and the so-called "superior pulmonary sulcus tumor" (which is probably a primary carcinoma from the pulmonary apex).

Harrington[3] surgically treated 47 extrapulmonary intrathoracic growths, of which 26 were benign and 21 malignant. Of these growths 15 were considered to have originated from the spinal root or intercostal nerve sheaths and were grouped under the general term, perineural fibroblastoma. Eleven were classified pathologically as neurofibromas, 2 as cellular fibromas and 2 as fibrosarcomas, which probably were benign tumors originally but had undergone malignant change. Twelve were histologically designated teratomas, 5 of these as dermoid cysts because their structure consisted essentially of ectoderm, in another 4 the tissue elements were derived from all 3 of the germinal layers, and a 5th showed such a high degree of organoid structure that it was designated as a fetal parasite; the remaining 2 of this group were squamous cell epitheliomas, evidently primarily benign tumors that had undergone malignant change.

Two chondromas and 1 osteochondroma completed the series of benign lesions; 1 chondroma was practically within the thorax and was discernible in the anterior portion of the thorax because of the marked calcification of the growth; in the other a moderate sized external mass presented in the anterior wall of the thorax, but the major portion of the tumor was in the thorax and filled practically two-thirds of the thoracic cavity with chondromyxomatous material which was definitely encapsulated. The chondro-osteoma involved one entire rib from the sternum to the spine.

Six cases in the series were classified pathologically as endothelioma; 3 of these originated in the parietal pleura, 1 in the visceral pleura, 1 in the anterior mediastinum and 1 in the posterior mediastinum.

In 11 cases the tumors proved to be sarcoma; in 7 the tumor originated in the bony structures of the wall of the thorax and in 4 it had its origin in the ribs close to its attachment to the vertebra.

The benign tumors summarized were: neurofibroma, 11; cellular

fibroma, 2; dermoid cyst, 5; teratoma, 4; fetal parasite, 1; chondroma, 2; and chondro-osteoma, 1. Of the malignant lesions 2 fibrosarcomas were considered primarily benign perineural fibroblastomas that had undergone malignant change, 2 squamous cell epitheliomas as teratomas that had originated as benign tumors and had undergone malignant change. The remaining malignant tumors were: endothelioma, 6, and sarcoma, 11.

In his experience, roentgenography plays an important rôle in the recognition and differential diagnosis of these growths in many of which surgical treatment offers the greatest hope for complete eradication of the disease. The clinical manifestations of these tumors are often meager and rarely pathognomonic, although they are always of value when correlated with the roentgenologic findings in establishing a final diagnosis. A study of early cases has proved that a relatively high percentage of the lesions is benign, but he believes that these tumors are potentially malignant.

The roentgenologic technique suggested is similar to that already mentioned; also the use of radiation therapy as an aid in differential diagnosis.

As evidence that the perineural fibroblastomas (commonly neurofibroma) are the most silent tumors within the thorax when they are benign, he states that 4 of the 15 were incidental roentgenographic findings during the course of a general examination. When these tumors do produce symptoms they are usually pressure symptoms due to mechanical interference as a result of location and increasing size. If these tumors undergo malignant change, pain becomes a feature, rather marked and more severe at night. These growths were the most common in the posterior mediastinum in his series, 13 of the 15 were located here, one was a dumb-bell or hour-glass tumor situated in the posterior mediastinum and the spinal canal and one was situated in the lateral wall of the thorax.

Roentgenographically they usually present a circumscribed shadow, rounded in contour, with a sharp border, situated usually in the posterior mediastinum. Sometimes the tumor is lobulated, but the borders are practically always sharply outlined. In those cases in which the tumor arises within the intervertebral foramen or spinal canal, the pedicles and laminæ of the vertebræ on the affected side are eroded and may be completely destroyed. There is enlargement of the intervertebral foramen, and as the tumor enlarges in the posterior mediastinum, sufficient pressure may be exerted to produce widening of the intercostal spaces and pressure erosion of adjacent ribs.

The lesion most commonly to be considered in the differential diagnosis of this group of tumors is aneurysm of the arch or descending portion of the aorta; roentgenoscopic examination of the thorax will usually determine whether the shadow is expansile or non-expansile. Sarcoma originating from the vertebræ or ribs can usually be differentiated because of the more extreme pain and the infiltrating destructive type of erosion of the involved ribs and vertebræ. Endotheliomas originating in the posterior mediastinum in early cases may be difficult to differentiate from neurofibromas, as endotheliomas are practically symptomless, in later cases their roentgenographic image is irregular in outline and the pleural effusion may be bloody. Pleural effusion

may be associated with any of these tumors, although it is not common. A tumor may be the cause of a pleural effusion and a benign tumor may be associated with a bloody effusion.

The teratoma group are the most common type of tumors in the anterior mediastinum; 11 of the 12 tumors in his series originated here. In 5 cases the tumor extended into the left thoracic cavity, in 4 into the right, and in 1 into both the right and the left thoracic cavities. The fetal parasite was confined to the anterior and superior mediastinum and presented just above the suprasternal notch. In the remaining case the tumor apparently originated in the right side of the diaphragm, and it may have originated from cell occlusion with improper fusion of the septum transversum and pleuroperitoneal membrane at the time of closure of the diaphragm. The usual clinical course in these cases is essentially that of an inflammatory lesion, consisting of pain in the mediastinum and dyspnea, and with a sense of pressure, often associated with a sore throat, which is commonly diagnosed clinically as pleurisy and pneumonia.

The roentgenologic manifestations of these growths are not as clear cut as those of other types of tumor and, even after the most exhaustive roentgenologic study, a definite diagnosis cannot be established. One of the main reasons for this difficulty is the marked inflammatory reaction which is often present, which produces a change simulating an inflammatory or infiltrating type of lesion in the structures surrounding the growth, often obscuring the definite outline of the tumor. The outline of the tumor may be hazy and infiltrating in character when viewed in one plane, but may show a rounded contour when viewed in another. Some may be cystic, and a definite fluid level may be visualized with its surrounding sac. On roentgenoscopic examination most of the growths present a transmitted pulsation due to their attachment to the pericardium at the base of the great vessels and great care must be exercised in differentiating these lesions from aneurysms of the arch or descending aorta.

Radiotherapy as a therapeutic test is often of aid in establishing a diagnosis by ruling out the presence of lymphoblastoma, which is one of the most common tumors to be considered in the differential diagnosis. Other conditions to be considered in the differential diagnosis are thymoma, substernal goiter and mediastinal abscess. There is no distinctive roentgenologic manifestation of endotheliomas, because of the great variation in size and character roentgenography has its greatest value in determining the extent and exact situation of the growth and in ruling out the complications that might contraindicate surgical intervention.

The outstanding symptom associated with sarcoma is pain, first intermittent in character and later becoming more or less constant; it is often more noticeable at night, and usually severe in type. The roentgenographic image shows dissolution of the bone contour, destruction of bone and secondary involvement of the surrounding soft tissues. In cases where neurofibroma has undergone malignant change, it may be impossible to make a definite diagnosis on roentgenologic findings or clinical symptoms.

Although roentgenologic studies of the thorax may be said to give the most important evidence in the clinical diagnosis of intrathoracic

tumors, they are of even greater importance in those cases which are considered for surgical treatment, not only for their assistance in the selection of operable growths, but also because of their aid in determining the most accessible type of approach to the tumor as well as the presence of conditions that might after operation become complications.

In a study of aneurysms of the innominate artery it was quite apparent that the diagnosis of aortitis must first be made. Warfield[6] found they do not occur without involvement of the aorta. The innominate aneurysm can be described as a superior mediastinal tumor arising on the right side at the upper level of the arch of the aorta and extending above the inner end of the clavicle. In extremely large aneurysms the shadow will extend over the left side. Compression of the trachea is a constant finding, displacement of the trachea to the left is not common. This compression, together with constant beating against the trachea, frequently produces decubitus ulcers. Expansile pulsations were elicited in only 1 of 20 cases, organized thrombus was found in the aneurysmal sac in 12 cases that were autopsied. Transmitted pulsation was seen in nearly every case. In differential diagnosis, a saccular aneurysm arising from the upper portion of the right aortic arch lacks the characteristic semicircular contour of an aneurysm of the innominate artery. It does not produce compression of the trachea nor does it present a palpable transmitted pulsating mass in the supraclavicular space. A unilateral substernal thyroid on the right side depresses the arch of the aorta downward and displaces the trachea to the left, widens from below upward, moves with the trachea and shows no transmitted pulsation. Dermoid cyst and tuberculosis rarely cast similar shadows.

Cysts of the Lung. Dubrow[1] reviewed the literature on congenital cysts of the lung and grouped these lesions under two divisions: (1) symptomatic and (2) asymptomatic. The latter embraces those solitary or multiple cysts with an open bronchial connection which is frequently discovered during roentgenographic examination for some other condition. The theories of their etiology explain to an extent the roentgenologic findings. Defective embryologic development of the bronchi results in complete or incomplete stenosis of the main bronchus or bronchi, usually of the upper lobe, with distal dilatation of the end bronchus; defective embryologic development of the areolar tissue (alveolar agenesis) which leaves the bronchi unsupported and causes them to be unduly dilated; and defective embryologic development of the lymph vessel systems of the corresponding lung occur. The cysts may be filled with fluid if the deformed bronchus is completely occluded, if incompletely stenosed they will contain air.

The condition may simulate bronchiectasis, pulmonary atelectasis and spontaneous pneumothorax. Lipiodol injection will demonstrate extensive sacculation in contradistinction to acquired massive pulmonary atelectasis in cases in which the main bronchus is completely obstructed. The roentgenogram in cystic lung fails to show any evidence of collapsed lung, the entrapped air being intrapulmonary. Cysts of the lung may be solitary or multiple, or one entire lung may be the seat of cystic degeneration. Schenck and Stein[5] reported a case of a solitary non-expansile fluid cyst in an infant 5 weeks old with no

symptoms referable to the chest. During a bout of vigorous coughing, the infant raised some thick, tenacious fluid. Roentgenographic examination revealed a horizontal fluid level with air above, which suggested a rupture of the cyst into a neighboring bronchus or bronchiole. Finally the cyst, entirely replaced by air, collapsed and the lesion spontaneously disappeared.

Before the advent of roentgenography the condition was seldom, if ever, recognized during life. Occasionally it is necessary to induce a pneumothorax to establish the diagnosis of congenital cystic lung. Diaphragmatic hernia or eventration can readily be excluded by roentgenoscopic examination after the oral administration of barium.

CHARLES G. SUTHERLAND, M.D.

REFERENCES.

1. Dubrow, J. L.: Congenital Cyst of the Lung, Radiology, **24**, 480, 1935.
2. Evans, W. A., and Witwer, E. R.: A Roentgen Consideration of Mediastinal Tumors, Ibid., p. 463.
3. Harrington, S. W.: The Value of Roentgen Rays in the Diagnosis and Surgical Treatment of Extrapulmonary Intrathoracic Tumors, Am. J. Roentgenol. and Rad. Ther., **33**, 340, 1935.
4. Pierce, C. B.: Extra-pulmonary Tumors of the Thorax, Radiology, **24**, 467, 1935.
5. Schenck, S. G., and Stein, J. L.: Congenital Lung Cysts in Infants and Children, Ibid., p. 420.
6. Warfield, C. H.: Roentgen Diagnosis of Aneurysms of the Innominate Artery, Am. J. Roentgenol. and Rad. Ther., **33**, 350, 1935.

Notice to Contributors.—Manuscripts intended for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES, and correspondence, should be sent to the Editor, DR. EDWARD B. KRUMBHAAR, School of Medicine, University of Pennsylvania, Philadelphia, Pa.

Articles are accepted for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES exclusively.

All manuscripts should be typewritten on one side of the paper only, and should be double spaced with liberal margins. The author's chief position and, when possible, the Department from which the work is produced should be indicated in the subtitle. Illustrations accompanying articles should be numbered and have captions bearing corresponding numbers. For identification they should also have the author's name written on the margin. The recommendations of the American Medical Association Style Book should be followed. It is important that references should be at the end of the articles and should be complete, that is, author's name, journal, volume, page and year (in Arabic numbers). Titles can be included for less than 25 references.

Return postage should accompany all manuscripts but will be returned to the author if the manuscript is accepted.

Two hundred and fifty reprints, with covers, are furnished gratis; additional reprints may be had in multiples of 250 at the expense of the author. They should be asked for when the galley proofs are returned.

Contributions in a foreign language, if found desirable for the JOURNAL, will be translated at its expense.